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AJDC Is 80 Years Old: From Pedology to Pediatrics

V. A. Fulginiti

Surfactant Replacement Therapy in Respiratory Distress Syndrome: Meta-analysis of Clinical Trials of Single-Dose Surfactant Extracts

H. M. Hennes, M. B. Lee, A. A. Rimm, D. L. Shapiro

Cat-Scratch Disease: Acute Encephalopathy and Other Neurologic Manifestations

H. A. Carithers, A. M. Margileth

Lumbar Puncture Frequency and Cerebrospinal Fluid Analysis in the Neonate

J. Schwersenski, L. McIntyre, C. R. Bauer

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S. Reif, D. G. Sloven, E. Lebenthal

Women in Medicine: Fantasies, Dreams, Myths, and Realities

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AMERICAN JOURNAL OF
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AJDC

Vol 145 **No. 1** **JANUARY 1991**

EDITORIAL

AJDC Is 80 Years Old: From Pedology to Pediatrics 11
Vincent A. Fulginiti, MD, New Orleans, La

THE PEDIATRIC FORUM

1991 Annual Meeting 26

Characteristics of Perinatal Cocaine-Exposed Infants With Necrotizing Enterocolitis 26
Gregory J. Downing, DO; Stanley R. Horner, DO; Howard W. Kilbride, MD, Kansas City, Mo

Current Social Practices Leading to Water Intoxication in Infants 27
Annabelle Schaeffer, MD, Stuart Ditchek, MD, Brooklyn, NY

Alkaline Urine Is Associated With Eating Disorders 28
Martha R. Arden, MD; Lauren Budow, MD; Douglas W. Bunnell, PhD; Michael P. Nussbaum, MD; I. Ronald Shenker, MD; Marc S. Jacobson, MD, New Hyde Park, NY

Major Congenital Neurologic Malformations 30
CPT Brian D. Ryals, MC, USA, Thomas E. Wiswell, MD, Washington, DC

EDITORIALS

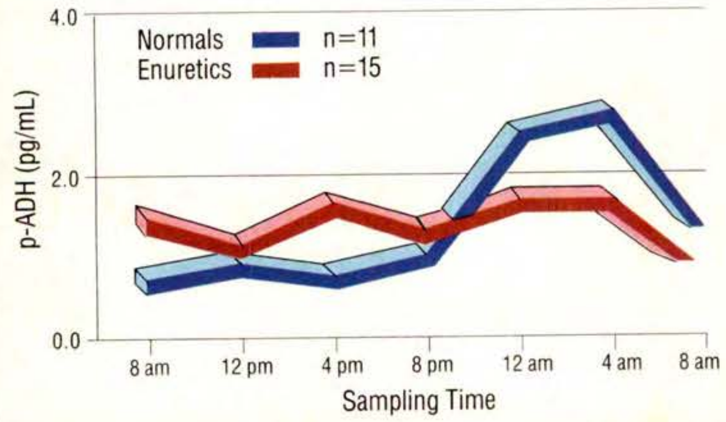
Status Report on Phenylketonuria Treatment: 1990 33
C. Charlton Mabry, MD, Lexington, Ky

Development, Growth, and Cardiac Surgery 33
John E. Mayer, Jr, MD, Boston, Mass

Continued on page 5.

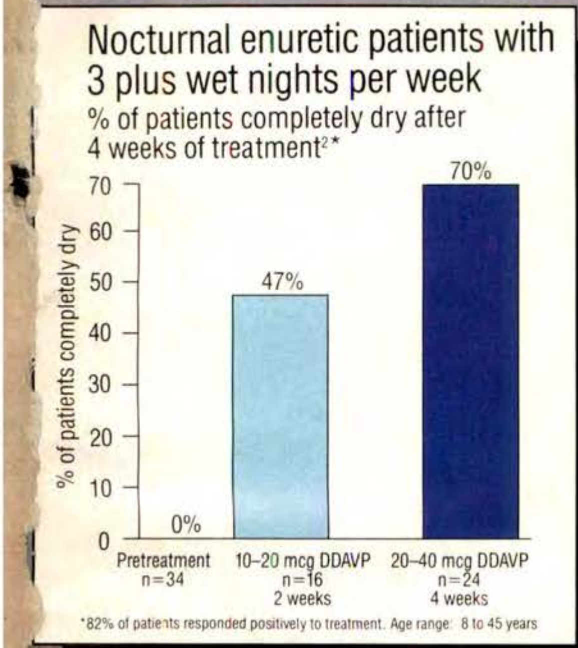
Landmark study concludes: Enuretic children may lack diurnal rhythm of ADH common in non-enuretic children[1]

Mean diurnal variation in plasma antidiuretic hormone (p-ADH) between normal and enuretic children[1]



The ADH Deficit

The first physiologic treatment for nocturnal enuresis


Nocturnal enuretic patients with 3 plus wet nights per week

% of patients completely dry after 4 weeks of treatment[2]*

*82% of patients responded positively to treatment. Age range: 8 to 45 years

- DDAVP Nasal Spray, a synthetic analog of naturally occurring ADH, provides physiologic control of nighttime urine production in children 6 years of age or older[1-4]
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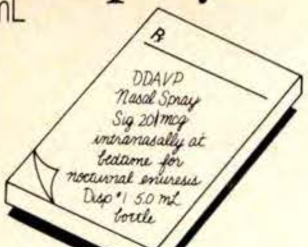

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CONTRAINDICATION: Known hypersensitivity to DDAVP

WARNINGS: 1. For intranasal use only. 2. In very young and elderly patients in particular, fluid intake should be adjusted in order to decrease the potential occurrence of water intoxication and hyponatremia.

PRECAUTIONS:

General: DDAVP at high dosage has infrequently produced a slight elevation of blood pressure, which disappeared with a reduction in dosage. The drug should be used with caution in patients with coronary artery insufficiency and/or hypertensive cardiovascular disease because of possible rise in blood pressure.

Primary Nocturnal Enuresis: If changes in the nasal mucosa have occurred, unreliable absorption may result. DDAVP intranasal solution should be discontinued until the nasal problems resolve.

Information for Patients: Patients should be informed that the bottle accurately delivers 50 doses of 10 mcg each. Any solution remaining after 50 doses should be discarded since the amount delivered thereafter may be substantially less than 10 mcg of drug. No attempt should be made to transfer remaining solution to another bottle. Patients should be instructed to read accompanying directions on use of the spray pump carefully before use.

Laboratory Tests: For the healthy patient with primary nocturnal enuresis, serum electrolytes should be checked at least once if therapy is continued beyond 7 days.

DRUG INTERACTIONS: Although the pressor activity of DDAVP is very low compared to the antidiuretic activity, use of large doses of DDAVP with other pressor agents should only be done with careful patient monitoring.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY: Teratology studies in rats have shown no abnormalities. No further information is available.

PREGNANCY—CATEGORY B: Reproduction studies performed in rats and rabbits with doses up to 12.5 times the human intranasal dose (i.e. about 125 times the total adult human dose given systemically) have revealed no evidence of harm to the fetus due to desmopressin acetate. There are several publications of management of diabetes insipidus in pregnant women with no harm to the fetus reported; however, no controlled studies in pregnant women have been carried out. Published reports stress that, as opposed to preparations containing the natural hormones, DDAVP (desmopressin acetate) in antidiuretic doses has no uterotonic action, but the physician will have to weigh possible therapeutic advantages against possible dangers in each individual case.

NURSING MOTHERS: There have been no controlled studies in nursing mothers. A single study in a postpartum woman demonstrated a marked change in plasma, but little if any change in assayable DDAVP in breast milk following an intranasal dose of 10 mcg.

PEDIATRIC USE: Primary Nocturnal Enuresis: DDAVP has been used in childhood nocturnal enuresis. Short-term (4-8 weeks) DDAVP administration has been shown to be safe and modestly effective in children aged 6 years or older with severe childhood nocturnal enuresis. Adequately controlled studies with intranasal DDAVP in primary nocturnal enuresis have not been conducted beyond 4-8 weeks. The dose should be individually adjusted to achieve the best results.

There are reports of an occasional change in response with time, usually greater than 6 months. Some patients may show a decreased responsiveness, others a shortened duration of effect. There is no evidence this effect is due to the development of binding antibodies but may be due to a local inactivation of the peptide.

ADVERSE REACTIONS: Infrequently, high dosages have produced transient headache and nausea. Nasal congestion, rhinitis and flushing have also been reported occasionally along with mild abdominal cramps. These symptoms disappeared with reduction in dosage. Nosebleed, sore throat, cough and upper respiratory infections have also been reported.

The following table lists the percent of patients having adverse experiences without regard to relationship to study drug from the pooled pivotal study data for nocturnal enuresis.

ADVERSE REACTION	**PLACEBO (N=59)** %	**DDAVP 20 mcg (N=60)** %	**DDAVP 40 mcg (N=61)** %
BODY AS A WHOLE			
Abdominal Pain	0	2	2
Asthenia	0	0	2
Chills	0	0	2
Headache	0	2	5
Throat Pain	2	0	0
NERVOUS SYSTEM			
Depression	2	0	0
Dizziness	0	0	3
RESPIRATORY SYSTEM			
Epistaxis	2	3	0
Nostril Pain	0	2	0
Respiratory Infection	2	0	0
Rhinitis	2	8	3
CARDIOVASCULAR SYSTEM			
Vasodilation	2	0	0
DIGESTIVE SYSTEM			
Gastrointestinal Disorder	0	2	0
Nausea	0	0	2
SKIN & APPENDAGES			
Leg Rash	2	0	0
Rash	2	0	0
SPECIAL SENSES			
Conjunctivitis	0	2	0
Edema Eyes	0	2	0
Lachrymation Disorder	0	0	2

OVERDOSAGE: See adverse reactions above. In case of overdosage, the dose should be reduced, frequency of administration decreased, or the drug withdrawn according to the severity of the condition. There is no known specific antidote for DDAVP.

An oral LD_{50} has not been established. An intravenous dose of 2 mg/kg in mice demonstrated no effect.

HOW SUPPLIED: A 5 mL bottle with spray pump delivering 50 doses of 10 mcg (NDC 0075-2450-02). Keep refrigerated at 36°-46°F (2°-8°C). When traveling, product will maintain stability for up to 3 weeks when stored at room temperature, 72°F (22°C).

See product circular for full prescribing information. Rev. 6/89

1. Rittig S, Knudsen UB, Nørgaard JP, et al: Abnormal diurnal rhythm of plasma vasopressin and urinary output in patients with enuresis. *Am J Physiol* 1989;25(4):F664-F671. 2. Rittig S, Knudsen UB, Sørensen S, et al: Long-term double-blind cross-over study of desmopressin intranasal spray in the management of nocturnal enuresis. In: Meadow SR, ed. *Desmopressin in Nocturnal Enuresis: Proceedings of an International Symposium.* England: Horus Medical Publications; 1988:43-55. 3. Dimson SB: DDAVP and urine osmolality in refractory enuresis. *Arch Dis Child* 1986;61:1104-1107. 4. Data on file, Rhône-Poulenc Rorer Pharmaceuticals Inc. 5. Richardson DW, Robinson AG: Diagnosis and treatment: Drugs five years later: Desmopressin. *Ann Intern Med* 1985;103:228-239.

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INDEX TO ADVERTISERS

B F Ascher & Company, Inc 21

Burroughs Wellcome Company 48A-B

Children's Hospital of the King's Daughters 109

Fisons Corporation 7-8, 31-32

Lederle Laboratories 59-60

McNeil Consumer Products Company .... 9-10, 64A-B, Cover 3
Mead Johnson Nutritional Division .... Cover 2, 25

Nemours Children's Clinic 8

Phoenix Children's Hospital 109

A. H. Robins Company 53
Rorer Pharmaceuticals 2-4

Wyeth-Ayerst Laboratories .... Cover 4

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AMERICAN JOURNAL OF DISEASES OF CHILDREN

ARTICLES

Intellectual Development in 12-Year-Old Children Treated for Phenylketonuria 35
Colleen G. Azen, MS; Richard Koch, MD; Eva Gross Friedman, Los Angeles, Calif; Stanley Berlow, MD, Madison, Wis; James Coldwell, MD, Tulsa, Okla; Wilma Krause, MD, Iowa City, Iowa; Reuben Matalon, MD, PhD, Chicago, Ill; Edward McCabe, MD, PhD, Denver, Colo; Margaret O'Flynn, MD, Los Angeles, Calif; Raymond Peterson, MD, San Diego, Calif; Bobbye Rouse, MD, Galveston, Tex; C. Ronald Scott, MD, Seattle, Wash; Bernice Sigman, MD, David Valle, MD, Baltimore, Md; Robert Warner, MD, Buffalo, NY

Follow-up of Patients Who Underwent Arterial Switch Repair for Transposition of the Great Arteries 40
Julita C. Mendoza, MD; Shirley A. Wilkerson, MD, PhD; Anabel H. Reese, MEd, Louisville, Ky

Elevated Plasma Norepinephrine Levels in Infants of Substance-Abusing Mothers 44
Sally L. Davidson Ward, MD; Sally Schuetz, RN, CPNP; Laura Wachsman, MD; Xylena D. Bean, MD; Daisy Bautista; Sue Buckley; Sabitha Sehgal, MD; David Warburton, MB, MRCP, Los Angeles, Calif

SPECIAL CONTRIBUTION

Women in Medicine: Fantasies, Dreams, Myths, and Realities 49
Catherine DeAngelis, MD, Baltimore, Md

ARTICLES

Lumbar Puncture Frequency and Cerebrospinal Fluid Analysis in the Neonate 54
Jeffrey Schwersenski, MD; Lester McIntyre, MD; Charles R. Bauer, MD, Miami, Fla

Family History Fails to Identify Many Children With Severe Hypercholesterolemia 61
Thomas J. Starc, MD; Peter F. Belamarich, MD; Steven Shea, MD; Beth E. Dobrin-Seckler, RD; Ralph B. Dell, MD; Welton M. Gersony, MD; Richard J. Deckelbaum, MD, New York, NY

Acute Osteomyelitis in Children: Reassessment of Etiologic Agents and Their Clinical Characteristics 65
Howard Faden, MD, Mauro Grossi, MD, Buffalo, NY

Pneumococcal Osteomyelitis and Arthritis in Children: A Hospital Series and Literature Review 70
Norman M. Jacobs, MD, Chicago, Ill

Influence of Otitis Media on the Correlation Between Rectal and Auditory Canal Temperatures 75
Thomas E. Terndrup, MD, Agnes Wong, MD, Syracuse, NY

EDUCATIONAL INTERVENTIONS

School Health Training During Pediatric Residency 79
Virginia N. Niebuhr, PhD; David P. McCormick, MD; Stephen E. Barnett, MD, Galveston, Tex

Continued on page 6.

AMERICAN JOURNAL OF DISEASES OF CHILDREN

ARTICLES

Nevus Flammeus: Discordance in Monozygotic Twins 85
Raanan Shamir, MD; Gertrude Kohn, MD;
Aryeh Metzker, MD, Tel Aviv, Israel

Neural Arch Stenosis and Spinal Cord Injury in Thanatophoric Dysplasia 87
Ona Marie Faye-Petersen, MD, A. S. Knisely, MD, Salt Lake City, Utah

Marfanoid Children: Etiologic Heterogeneity and Cardiac Findings 90
Shawky Tayel, MD; Thaddeus W. Kurczynski, MD, PhD;
Marc Levine, MD; Ernest Brookfield, MD; Robert Ehrlich, MD;
James R. Hennessy, MD; Martin M. DeBeukelaer, MD, Toledo, Ohio

Differences in Expression of Cystic Fibrosis in Blacks and Whites 94
Susanna A. McColley, MD; Beryl J. Rosenstein, MD;
Garry R. Cutting, MD, Baltimore, Md

Cat-Scratch Disease: Acute Encephalopathy and Other Neurologic Manifestations 98
Hugh A. Carithers, MD, Jacksonville, Fla;
A. M. Margileth, MD, Bethesda, Md

Surfactant Replacement Therapy in Respiratory Distress Syndrome: Meta-analysis of Clinical Trials of Single-Dose Surfactant Extracts 102
Halim M. Hennes, MD; Martha B. Lee, PhD;
Alfred A. Rimm, PhD, Milwaukee, Wis;
Donald L. Shapiro, MD, Rochester, NY

Gallstones in Children: Characterization by Age, Etiology, and Outcome 105
Shimon Reif, MD, Buffalo, NY; Daniel G. Sloven, MD, St Louis, Mo;
Emanuel Lebenthal, MD, Philadelphia, Pa

SPECIAL FEATURES

Radiological Case of the Month 111
CPT Michael E. Ruff, MC, USA;
MAJ W. Michael Southgate, MC, USA, Hawaii;
Beverly P. Wood, MD, Los Angeles, Calif

Picture of the Month 113
Jeffrey L. Loughead, MD; Francis Mimouni, MD;
Sue Schilling, RN, Cincinnati, Ohio;
Murray Feingold, MD, Brighton, Mass

1990 Reviewers for AJDC 115

REGULAR DEPARTMENTS

Index to Advertisers 4

Information for Authors 110

Classified Advertising 122

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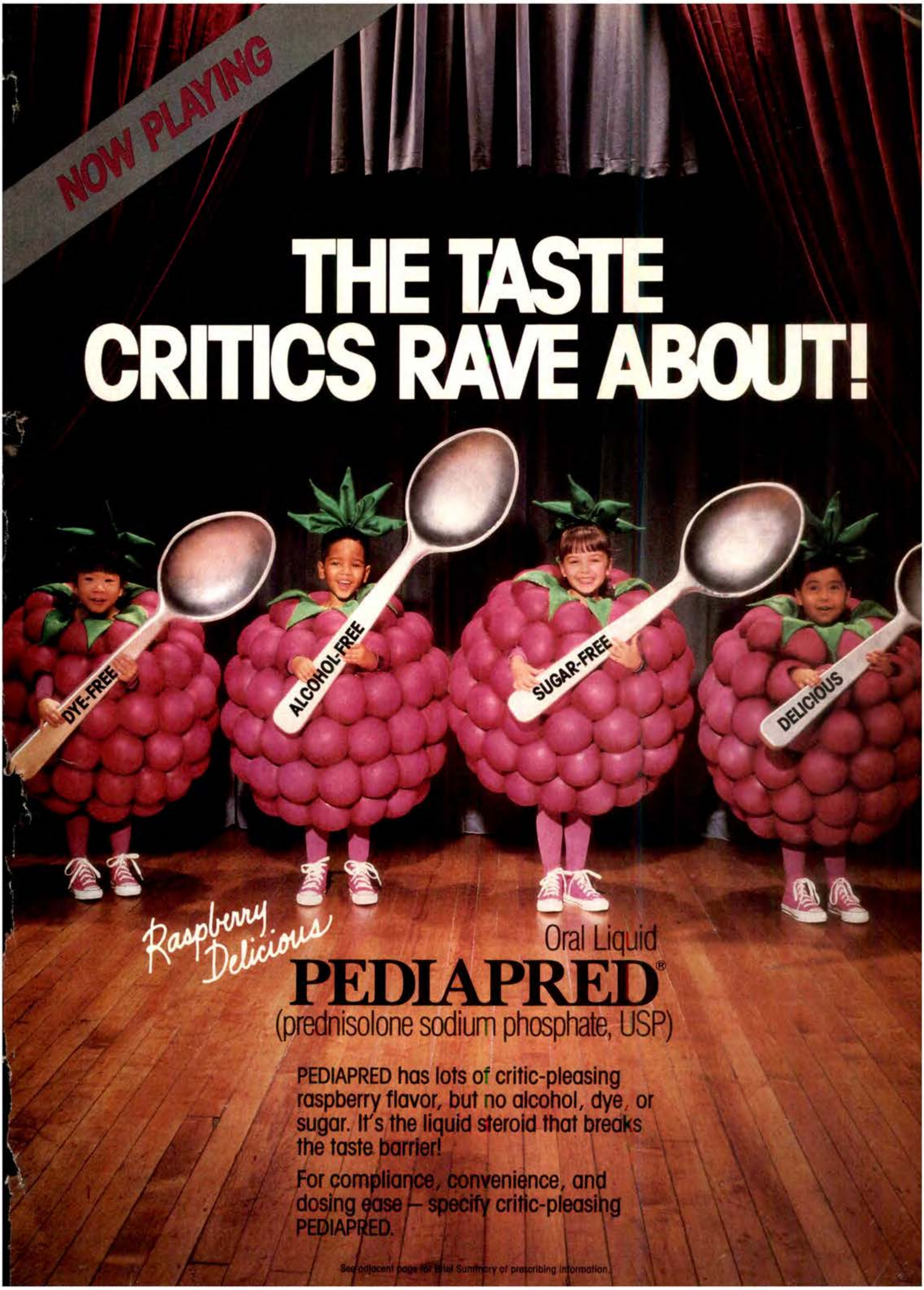

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CONTRAINDICATIONS: Systemic fungal infections.

WARNINGS: In patients on corticosteroid therapy subjected to unusual stress, increased dosage of rapidly acting corticosteroids before, during and after the stressful situation is indicated.

Corticosteroids may mask some signs of infection, and new infections may appear during their use. There may be decreased resistance and inability to localize infection when corticosteroids are used.

Prolonged use of corticosteroids may produce posterior subcapsular cataracts, glaucoma with possible damage to the optic nerves, and may enhance the establishment of secondary ocular infections due to fungi or viruses.

Average and large doses of hydrocortisone or cortisone can cause elevation of blood pressure, salt and water retention, and increased excretion of potassium. These effects are less likely to occur with the synthetic derivatives except when used in large doses. Dietary salt restriction and potassium supplementation may be necessary. All corticosteroids increase calcium excretion. **While on corticosteroid therapy patients should not be vaccinated against smallpox. Other immunization procedures should not be undertaken in patients who are on corticosteroids, especially on high doses, because of possible hazards of neurological complications and a lack of antibody response.**

The use of prednisolone in active tuberculosis should be restricted to those cases of fulminating or disseminated tuberculosis in which the corticosteroid is used for the management of the disease in conjunction with an appropriate antituberculous regimen.

If corticosteroids are indicated in patients with latent tuberculosis or tuberculin reactivity, close observation is necessary as reactivation of the disease may occur. During prolonged corticosteroid therapy these patients should receive chemoprophylaxis.

PRECAUTIONS: General: Drug-induced secondary adrenocortical insufficiency may be minimized by gradual reduction of dosage. This type of relative insufficiency may persist for months after discontinuation of therapy; therefore, in any situation of stress occurring during that period, hormone therapy should be reinstituted. Since mineralocorticoid secretion may be impaired, salt and/or a mineralocorticoid should be administered concurrently.

There is an enhanced effect of corticosteroids in patients with hypothyroidism and in those with cirrhosis.

Corticosteroids should be used cautiously in patients with ocular herpes simplex because of possible corneal perforation.

The lowest possible dose of corticosteroid should be used to control the condition under treatment, and when reduction in dosage is possible, the reduction should be gradual.

Psychic derangements may appear when corticosteroids are used, ranging from euphoria, insomnia, mood swings, personality changes, and severe depression, to frank psychotic manifestations. Also, existing emotional instability or psychotic tendencies may be aggravated by corticosteroids.

Aspirin should be used cautiously in conjunction with corticosteroids in hypoprothrombinemia.

Steroids should be used with caution in nonspecific ulcerative colitis, if there is a probability of impending perforation, abscess or other pyogenic infection; diverticulitis; fresh intestinal anastomoses; active or latent peptic ulcer; renal insufficiency; hypertension; osteoporosis; and myasthenia gravis.

Growth and development of infants and children on prolonged corticosteroid therapy should be carefully observed.

Although controlled clinical trials have shown corticosteroids to be effective in speeding the resolution of acute exacerbations of multiple sclerosis, they do not show that they affect the ultimate outcome or natural history of the disease. The studies do show that relatively high doses of corticosteroids are necessary to demonstrate a significant effect. (See DOSAGE AND ADMINISTRATION.)

Since complications of treatment with glucocorticoids are dependent on the size of the dose and the duration of treatment, a risk/benefit decision must be made in each individual case as to dose and duration of treatment and as to whether daily or intermittent therapy should be used.

Information for Patients: Patients should be warned not to discontinue the use of PEDIAPRED abruptly or without medical supervision, to advise any medical attendants that they are taking PEDIAPRED and to seek medical advice at once should they develop fever or other signs of infection.

Drug Interactions: Drugs such as barbiturates which induce hepatic microsomal drug metabolizing enzyme activity may enhance metabolism of prednisolone and require that the dosage of PEDIAPRED be increased.

Pregnancy: Pregnancy Category C - Prednisolone has been shown to be teratogenic in many species when given in doses equivalent to the human dose. There are no adequate and well controlled studies in pregnant women. PEDIAPRED should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Animal studies in which prednisolone has been given to pregnant mice, rats and rabbits have yielded an increased incidence of cleft palate in the offspring.

Nursing Mothers: Prednisolone is excreted in breast milk, but only to a small (less than 1% of the administered dose) and probably clinically insignificant extent. Caution should be exercised when PEDIAPRED is administered to a nursing woman.

ADVERSE REACTIONS:

Fluid and Electrolyte Disturbances
Sodium retention; fluid retention; congestive heart failure in susceptible patients; potassium loss; hypokalemic alkalosis; hypertension

Musculoskeletal
Muscle weakness; steroid myopathy; loss of muscle mass; osteoporosis; vertebral compression fractures; aseptic necrosis of femoral and humeral heads; pathologic fracture of long bones

Gastrointestinal
Peptic ulcer with possible perforation and hemorrhage; pancreatitis; abdominal distention; ulcerative esophagitis

Dermatologic
Impaired wound healing; thin fragile skin; petechiae and ecchymoses; facial erythema; increased sweating; may suppress reactions to skin tests

Metabolic
Negative nitrogen balance due to protein catabolism

Neurological
Convulsions; increased intracranial pressure with papilledema (pseudotumor cerebri) usually after treatment; vertigo; headache

Endocrine
Menstrual irregularities; development of cushingoid state; secondary adrenocortical and pituitary unresponsiveness, particularly in times of stress, as in trauma, surgery or illness; suppression of growth in children; decreased carbohydrate tolerance; manifestations of latent diabetes mellitus; increased requirements for insulin or oral hypoglycemic agents in diabetes

Ophthalmic
Posterior subcapsular cataracts; increased intraocular pressure; glaucoma; exophthalmos

OVERDOSAGE: The effects of accidental ingestion of large quantities of prednisolone over a very short period of time have not been reported, but prolonged use of the drug can produce mental symptoms, moon face, abnormal fat deposits, fluid retention, excessive appetite, weight gain, hypertrichosis, acne, striae, ecchymosis, increased sweating, pigmentation, dry scaly skin, thinning scalp hair, increased blood pressure, tachycardia, thrombophlebitis, decreased resistance to infection, negative nitrogen balance with delayed bone and wound healing, headache, weakness, menstrual disorders, accentuated menopausal symptoms, neuropathy, fractures, osteoporosis, peptic ulcer, decreased glucose tolerance, hypokalemia, and adrenal insufficiency. Hepatomegaly and abdominal distention have been observed in children.

Treatment of acute overdosage is by immediate gastric lavage or emesis. For chronic overdosage in the face of severe disease requiring continuous steroid therapy the dosage of prednisolone may be reduced only temporarily, or alternate day treatment may be introduced.

CAUTION: Federal law prohibits dispensing without prescription.

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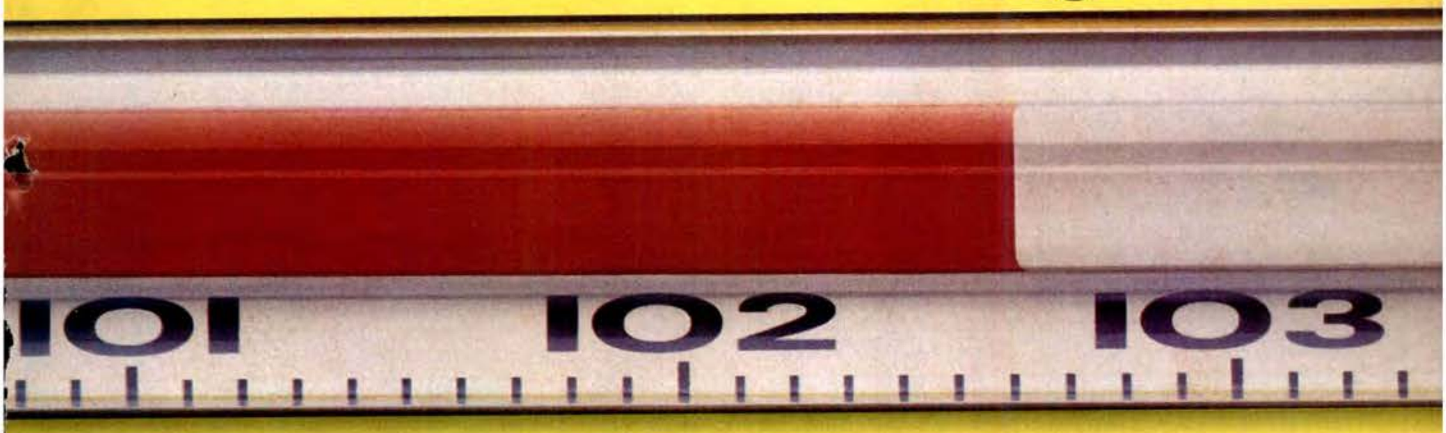

Superior reduction for fevers over 102.5°F

Proven efficacy
For reducing children's temperatures over 102.5°F, ibuprofen 10 mg/kg was proven more effective than acetaminophen 10 mg/kg.[1]

Longer duration of action for fevers over 102.5°F
For duration of fever relief, ibuprofen 10 mg/kg was proven more effective than acetaminophen 10 mg/kg —relief lasted up to 8 hours.[1,2]

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Please see brief summary of Prescribing Information on the next page.

References:
1. Walson PD et al. Ibuprofen, acetaminophen, and placebo treatment of febrile children. *Clin Pharmacol Ther.* 1989;46:9-17. 2. Data on file, McNeil Consumer Products Company.

Superior reduction for fevers over 102.5°F

PediaProfen™

Ibuprofen Suspension 100 mg/5 ml

The following is a brief summary only. Before prescribing, see complete prescribing information in **PediaProfen** labeling.

INDICATIONS AND USAGE: PediaProfen is indicated for the reduction of fever in patients aged 6 months and older, and for the relief of mild-to-moderate pain in patients aged 12 years and older.

CLINICAL PHARMACOLOGY: Controlled clinical trials comparing doses of 5 and 10 mg/kg ibuprofen and 10-15 mg/kg of acetaminophen have been conducted in children 6 months to 12 years of age with fever primarily due to viral illnesses. In these studies there were no differences between treatments in fever reduction for the first hour and maximum fever reduction occurred between 2 and 4 hours. Response after 1 hour was dependent on both the level of temperature elevation as well as the treatment. In children with baseline temperatures at or below 102.5°F, both ibuprofen doses and acetaminophen were equally effective in their maximum effect. In those children with temperatures above 102.5°F, the ibuprofen 10 mg/kg dose was more effective. By 6 hours children treated with ibuprofen 5 mg/kg tended to have recurrence of fever, whereas children treated with ibuprofen 10 mg/kg still had significant fever reduction at 8 hours. In control groups treated with 10 mg/kg acetaminophen, fever reduction resembled that seen in children treated with 5 mg/kg of ibuprofen, with the exception that temperature elevation tended to return 1-2 hours earlier.

CONTRAINDICATIONS: PediaProfen should not be used in patients who have previously exhibited hypersensitivity to ibuprofen, or in individuals with all or part of the syndrome of nasal polyps, angioedema and bronchospastic reactivity to aspirin or other nonsteroidal anti-inflammatory agents. Anaphylactoid reactions have occurred in such patients.

WARNINGS: Risk of GI Ulceration, Bleeding and Perforation with NSAID Therapy. Serious gastrointestinal toxicity such as bleeding, ulceration, and perforation, can occur at any time, with or without warning symptoms, in patients treated chronically with NSAID therapy. Although minor upper gastrointestinal problems, such as dyspepsia, are common, usually developing early in therapy, physicians should remain alert for ulceration and bleeding in patients treated chronically with NSAIDs even in the absence of previous GI tract symptoms. In patients observed in clinical trials of several months to two years duration, symptomatic upper GI ulcers, gross bleeding or perforation appear to occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for one year. Physicians should inform patients about the signs and/or symptoms of serious GI toxicity and what steps to take if they occur.

Studies to date have not identified any subset of patients not at risk of developing peptic ulceration and bleeding. Except for a prior history of serious GI events and other risk factors known to be associated with peptic ulcer disease, such as alcoholism, smoking, etc., no risk factors (e.g., age, sex) have been associated with increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less well than other individuals and most spontaneous reports of fatal GI events are in this population. Studies to date are inconclusive concerning the relative risk of various NSAIDs in causing such reactions. High doses of any NSAID probably carry a greater risk of these reactions, although controlled clinical trials showing this do not exist in most cases. In considering the use of relatively large doses (within the recommended dosage range), sufficient benefit should be anticipated to offset the potential increased risk of GI toxicity.

PRECAUTIONS: General: Blurred and/or diminished vision, scotomata, and/or changes in color vision have been reported. If a patient develops such complaints while receiving **PediaProfen**, the drug should be discontinued and the patient should have an ophthalmologic examination which includes central visual fields and color vision testing.

Fluid retention and edema have been reported in association with ibuprofen; therefore, the drug should be used with caution in patients with a history of cardiac decompensation or hypertension.

PediaProfen, like other nonsteroidal anti-inflammatory agents, can inhibit platelet aggregation, but the effect is quantitatively less and of shorter duration than that seen with aspirin. Ibuprofen has been shown to prolong bleeding time (but within the normal range) in normal subjects. Because this prolonged bleeding effect may be exaggerated in patients with underlying hemostatic defects, **PediaProfen** should be used with caution in persons with intrinsic coagulation defects and those on anticoagulant therapy.

Patients on **PediaProfen** should report to their physicians signs or symptoms of gastrointestinal ulceration or bleeding, blurred vision or other eye symptoms, skin rash, weight gain, or edema.

In order to avoid exacerbation of disease of adrenal insufficiency, patients who have been on prolonged corticosteroid therapy should have their therapy tapered slowly rather than discontinued abruptly when ibuprofen is added to the treatment program.

The antipyretic and anti-inflammatory activity of **PediaProfen** may reduce fever and inflammation, thus diminishing their utility as diagnostic signs in detecting complications of presumed noninfectious, noninflammatory painful conditions.

Since ibuprofen is eliminated primarily by the kidney, patients with significantly impaired renal function should be closely monitored and a reduction in dosage should be anticipated to avoid drug accumulation. Prospective studies on the safety of ibuprofen in patients with chronic renal failure have not been conducted.

Safety and efficacy of **PediaProfen** in children below the age of 6 months has not been established.

Pregnancy: Reproductive studies conducted in rats and rabbits at doses somewhat less than the maximal clinical dose did not demonstrate evidence of developmental abnormalities. However, animal reproduction studies are not always predictive of human response. As there are no adequate and well-controlled studies in pregnant women, this drug should be used during pregnancy only if clearly needed. Because of the known effects of nonsteroidal anti-inflammatory drugs on the fetal cardiovascular system (closure of ductus arteriosus), use during late pregnancy should be avoided. As with other drugs known to inhibit prostaglandin synthesis, an increased incidence of dystocia and delayed parturition occurred in rats. Administration of **PediaProfen** is not recommended during pregnancy.

ADVERSE REACTIONS: The most frequent type of adverse reaction occurring with ibuprofen is gastrointestinal. In controlled clinical trials, the percentage of adult patients reporting one or more gastrointestinal complaints ranged from 4% to 16%.

Adverse reactions occurring in 3% to 9% of patients treated with ibuprofen: nausea, epigastric pain, heartburn, dizziness, rash. *Adverse reactions occurring in 1% to 3% of patients:* diarrhea, abdominal distress, nausea and vomiting, indigestion, constipation, abdominal cramps or pain, fullness of GI tract, headache, nervousness, pruritus, tinnitus, decreased appetite, edema, fluid retention (generally responds promptly to drug discontinuation). Still other reactions (less than 1 in 100) have been reported, and are detailed in the full summary of prescribing information.

DOSAGE AND ADMINISTRATION: Shake well prior to administration.

Fever Reduction in Children 6 months to 12 years of age: Dosage should be adjusted on the basis of the initial temperature level (See CLINICAL PHARMACOLOGY for a description of the controlled clinical trial results). The recommended dose is 5 mg/kg if the baseline temperature is less than 102.5°F or 10 mg/kg if the baseline temperature is greater than 102.5°F. The duration of fever reduction is generally 6-8 hours and is longer with the higher dose. The recommended maximum daily dose is 40 mg/kg.

Mild to moderate pain: 400 mg every 4 to 6 hours as necessary for the relief of pain in adults.

In controlled analgesic clinical trials, doses of ibuprofen greater than 400 mg were no more effective than 400 mg dose.

HOW SUPPLIED: PediaProfen Ibuprofen Suspension 100 mg/5 ml (teaspoon)—
orange, berry-vanilla flavored

Bottles of 4 oz (120 ml)	NDC 0045-0469-04
Bottles of 16 oz (480 ml)	NDC 0045-0469-16

SHAKE WELL BEFORE USING. Store at room temperature.

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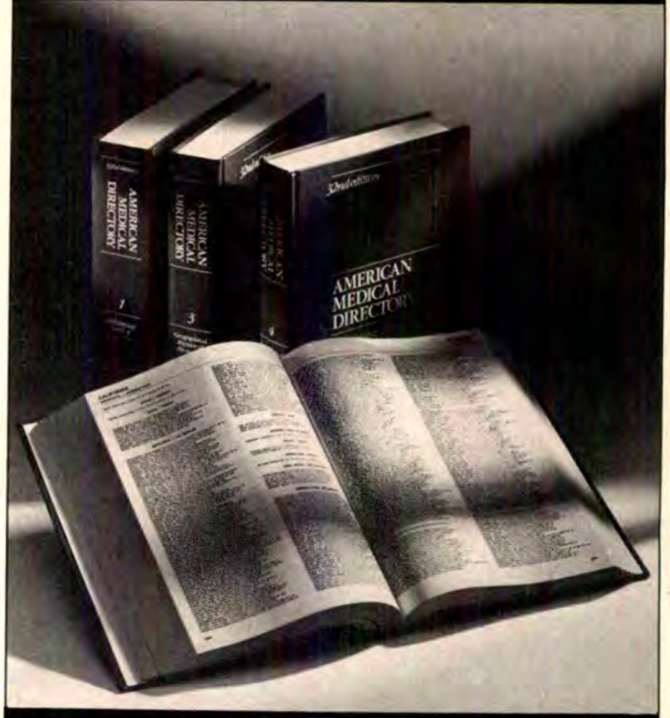
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AJDC Is 80 Years Old

From Pedology to Pediatrics

In 1911, the *American Journal of Diseases of Children* was initiated. The editorial board consisted of Abraham Jacobi (often referred to as the Father of Pediatrics), Frank Spooner Churchill, John Lovett Morse, William Fitch Cheney, Edwin E. Graham, and John Howland. If one looks at the first year of operation of the journal, one is struck with the similarity between the issues with which the pediatricians of that day were concerned and those that we deal with today. For example, in those first issues, meningitis, streptococcal infections, genetic disorders, nutritional topics, developmental research, hypertension, hemorrhagic diseases, and "modern" instrumentation for diagnosis and treatment were all present.

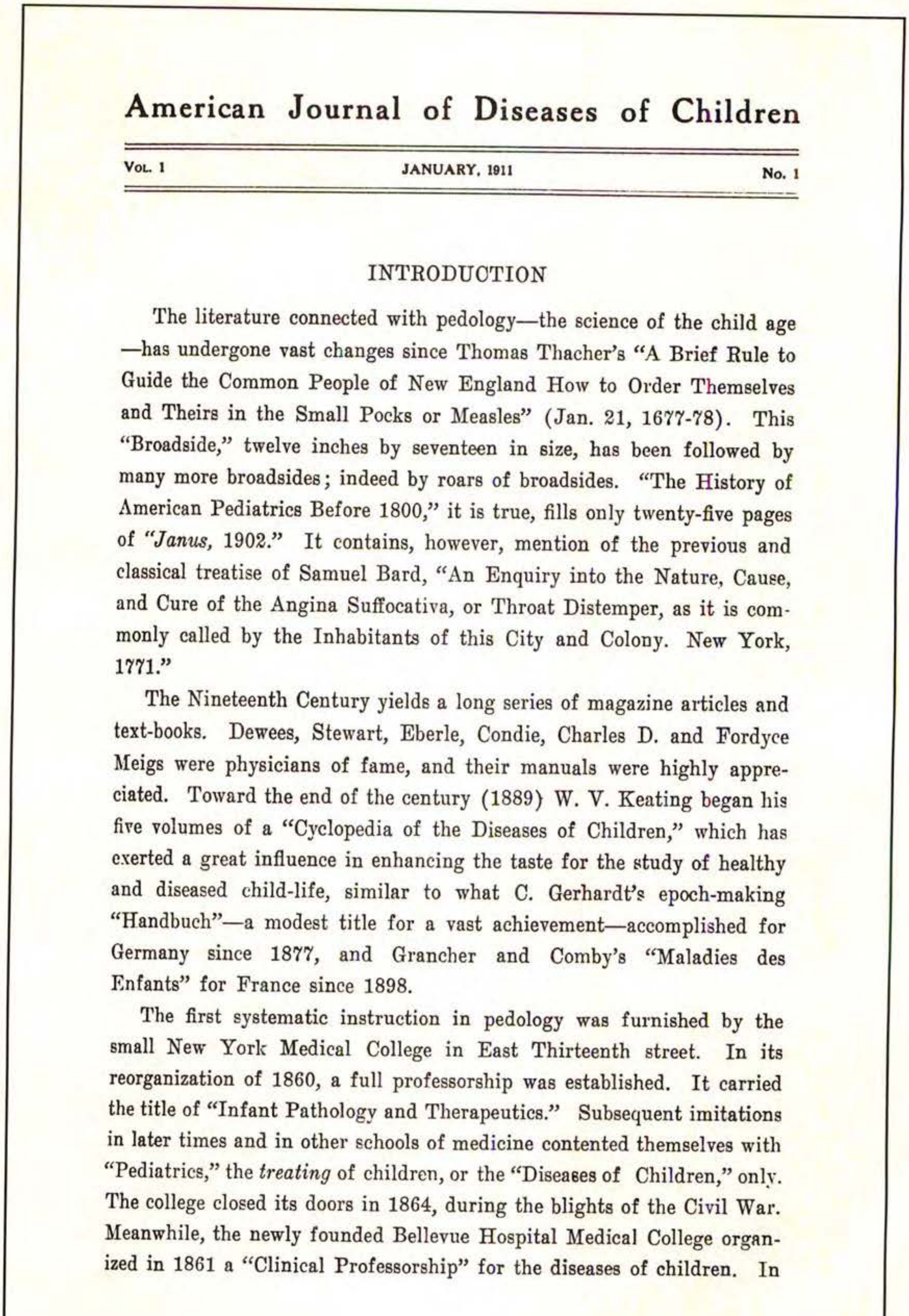
The biologic knowledge base was imperfect, and scant by our standards, but the questions asked were strikingly similar. What pathophysiologic processes underlie disease states? What is the best way to make a diagnosis? What is the best management for a given disorder? What is the best way to feed infants to ensure proper nutrition? What causes these odd disorders that develop in infants and children? What is the course of bone development? Each of these questions is at the base of the articles that appeared 80 years ago; they are still the basis of articles 80 years later, in this issue and in the remaining issues of this year. We continue the quest for new information, and *AJDC* continues in its perceived mission to disseminate answers to these pertinent questions to the best of our authors' knowledge.

In his introduction to the first issue in 1911, Dr Jacobi wrote, "Our present copious pediatric literature dates from about the middle of the last century. Extracts, reviews, and original contributions became plentiful; our weeklies, monthlies and quarterlies contained much that was and much that still is of value." I could have written those words today with a slight change in time frame! Dr Jacobi also lauded the development of a new discipline, pedology, which he defined as ". . . the science of the child age. . . . " He further directed readers to ". . . look on pediatrics not as a specialty, . . . but as that part of internal medicine and surgery which cannot be measured by the knowledge derived from and applied to the adult. . . ." Pediatrics has succeeded in that separation in the 80 years since Jacobi wrote that passage, and we have learned repeatedly that principles of biology and medicine are unique to the developing child and cannot be extrapolated from experience with adults. Dr Jacobi emphasized growth and development as singular characteristics that the budding specialty was to focus on and that the journal would give visibility to—he was again correct and prophetic. This fact seems second nature to us now, but in his day it was considered heretical by some.

AJDC played a role in that evolution by stressing observations and investigations that focused on the unique characteristics of childhood. For example, in the first issue, Fetterolf and Gittings of Philadelphia, Pa, focused on those thoracic anatomic features that conditioned the physical examination of a child in contrast to an adult. They outlined the enormous size of the thymus, the thinness of the chest wall, the relatively enlarged heart in the child's thorax than in the adult, and so on. Martha Wollstein of New York, NY, attempted to cultivate "influenza bacilli" from the cerebrospinal fluid of children with meningitis and inoculate mice, guinea pigs, rabbits, and monkeys. She produced meningitis in the simian model and detailed the factors that led to virulence, immune response, and disease production. Issac Abt described a child with "amaurotic family idiocy," complete with autopsy findings, which helped to define what we now know as Tay-Sachs disease. These all are examples of what Dr Jacobi was referring to when he defined pedology.

History is important to all of us; we ignore it at our peril. We need to know where we have been to know where we want to go. All of us connected with *AJDC* are proud that we are part of a historical thread that stretches back these 80 years, and that our journal has played its role in the development of "pedology" into the science and art of pediatrics. So we say "happy birthday to *AJDC*" and as temporary custodians of this important part of our discipline, we will strive to continue the tradition that Dr Jacobi and others inaugurated in January 1911. In celebration of that birthday and to remind us of our origins, we are reprinting Dr Jacobi's "Introduction" and the "Table of Contents" of the 1911 issues of *AJDC*.

Vincent A. Fulginiti, MD
Editor, *AJDC*
Dean's Office
Tulane University
School of Medicine
1430 Tulane Ave
New Orleans, LA 70112



American Journal of Diseases of Children

Vol. 1 JANUARY, 1911 No. 1

INTRODUCTION

The literature connected with pedology—the science of the child age—has undergone vast changes since Thomas Thacher's "A Brief Rule to Guide the Common People of New England How to Order Themselves and Theirs in the Small Pocks or Measles" (Jan. 21, 1677-78). This "Broadside," twelve inches by seventeen in size, has been followed by many more broadsides; indeed by roars of broadsides. "The History of American Pediatrics Before 1800," it is true, fills only twenty-five pages of "*Janus*, 1902." It contains, however, mention of the previous and classical treatise of Samuel Bard, "An Enquiry into the Nature, Cause, and Cure of the Angina Suffocativa, or Throat Distemper, as it is commonly called by the Inhabitants of this City and Colony. New York, 1771."

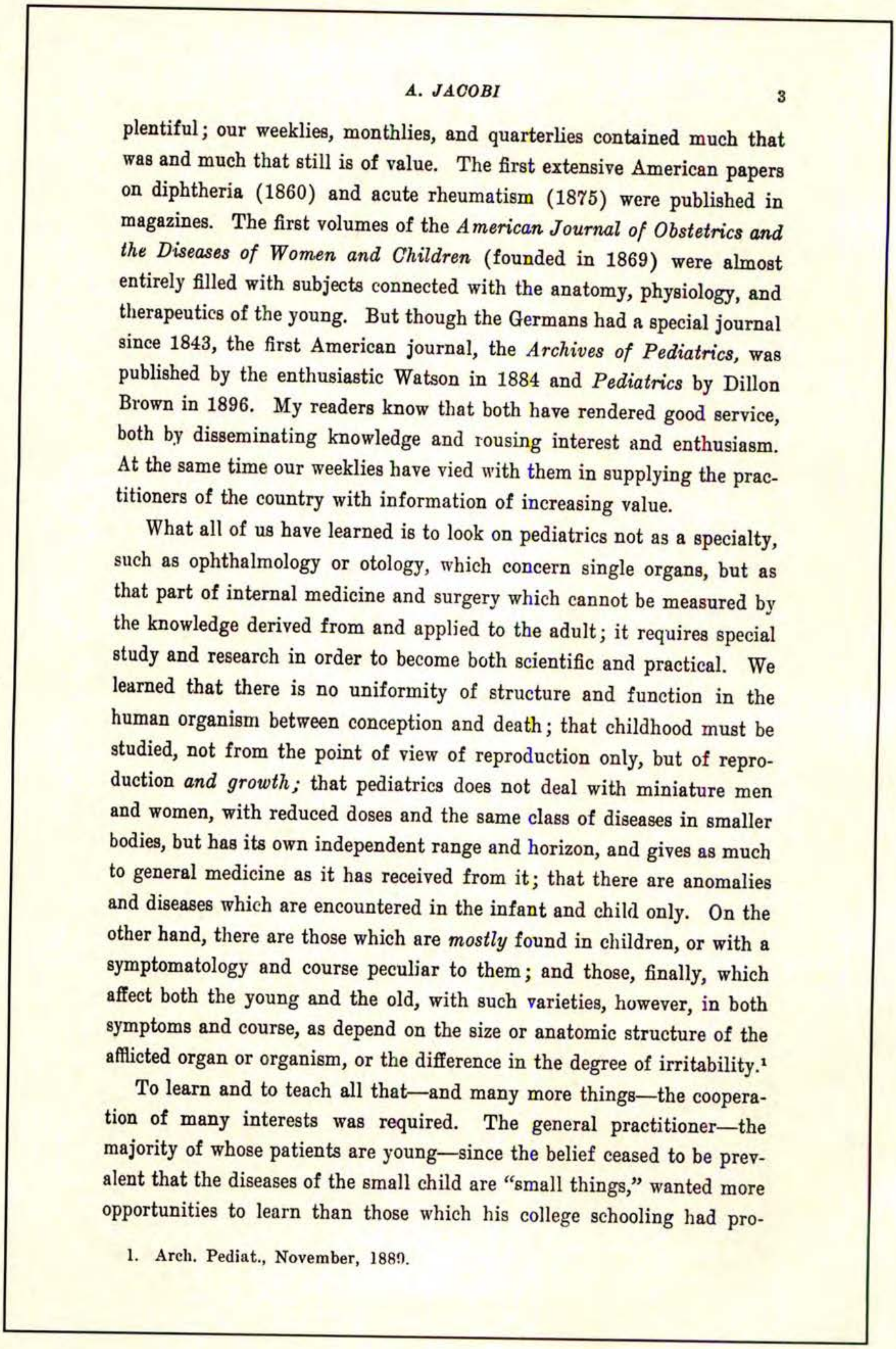
The Nineteenth Century yields a long series of magazine articles and text-books. Dewees, Stewart, Eberle, Condie, Charles D. and Fordyce Meigs were physicians of fame, and their manuals were highly appreciated. Toward the end of the century (1889) W. V. Keating began his five volumes of a "Cyclopedia of the Diseases of Children," which has exerted a great influence in enhancing the taste for the study of healthy and diseased child-life, similar to what C. Gerhardt's epoch-making "Handbuch"—a modest title for a vast achievement—accomplished for Germany since 1877, and Grancher and Comby's "Maladies des Enfants" for France since 1898.

The first systematic instruction in pedology was furnished by the small New York Medical College in East Thirteenth street. In its reorganization of 1860, a full professorship was established. It carried the title of "Infant Pathology and Therapeutics." Subsequent imitations in later times and in other schools of medicine contented themselves with "Pediatrics," the *treating* of children, or the "Diseases of Children," only. The college closed its doors in 1864, during the blights of the Civil War. Meanwhile, the newly founded Bellevue Hospital Medical College organized in 1861 a "Clinical Professorship" for the diseases of children. In that chair Dr. J. Lewis Smith displayed great industry and enthusiasm, and did much to enlighten the profession in regard to both the difficulties and the importance of the comparatively new doctrine. Another clinical professorship of the same nature was established in 1865 by the University Medical College, and in 1870 by the College of Physicians and Surgeons.

Since that time, the example given by New York has been followed by a large number of the medical schools in the country. Very few of them founded full professorships endowed with the full rights and duties awarded to the rest of the teachers who connected themselves with a medical school or the medical faculty of a university. Harvard was the first to see the light. Though the recognition came late and is far from being universal, we are still ahead of the present status of pedology in the curricula of most European medical schools. Germany, to this day, has few full professorships for instruction in the diseases of children. Indeed, its great teacher and classical writer, Eduard Henoch (1881) closed in 1893 his academic career with the title of a mere "Extraordinary Professor." When, a few weeks ago, however, he was taken away, 90 years old, he had the satisfaction of knowing that there was at last a breach in the short-sighted conservatism of German universities, and that at last a few full chairs of pedology had been established.

Great men like him are scarce in any part of medicine. To excel in close observation, logical reasoning, and elegant and precise diction, together with the faculty of teaching, is given to few men. Charles West in England (1848), Rilliet and Barthez in Switzerland and France (1843), belong to that class and deserve with Henoch the name of classical authors and instructors. They have passed away, but they have been followed by successors, few, it is true, of equal rank, but very numerous and many of them meritorious writers. If but few approach them, the multitude of those who have something to say—and the much greater multitude who say it anyhow—have made the study of the child and its diseases popular and interesting. If it so happens that too much is published, that is only a repetition of the experience of other doctrines in our science and art. Guttenberg's art could not have been discovered by everybody who is satisfied with utilizing or abusing it.

Our present copious pediatric literature dates from about the middle of the last century. Extracts, reviews, and original contributions became

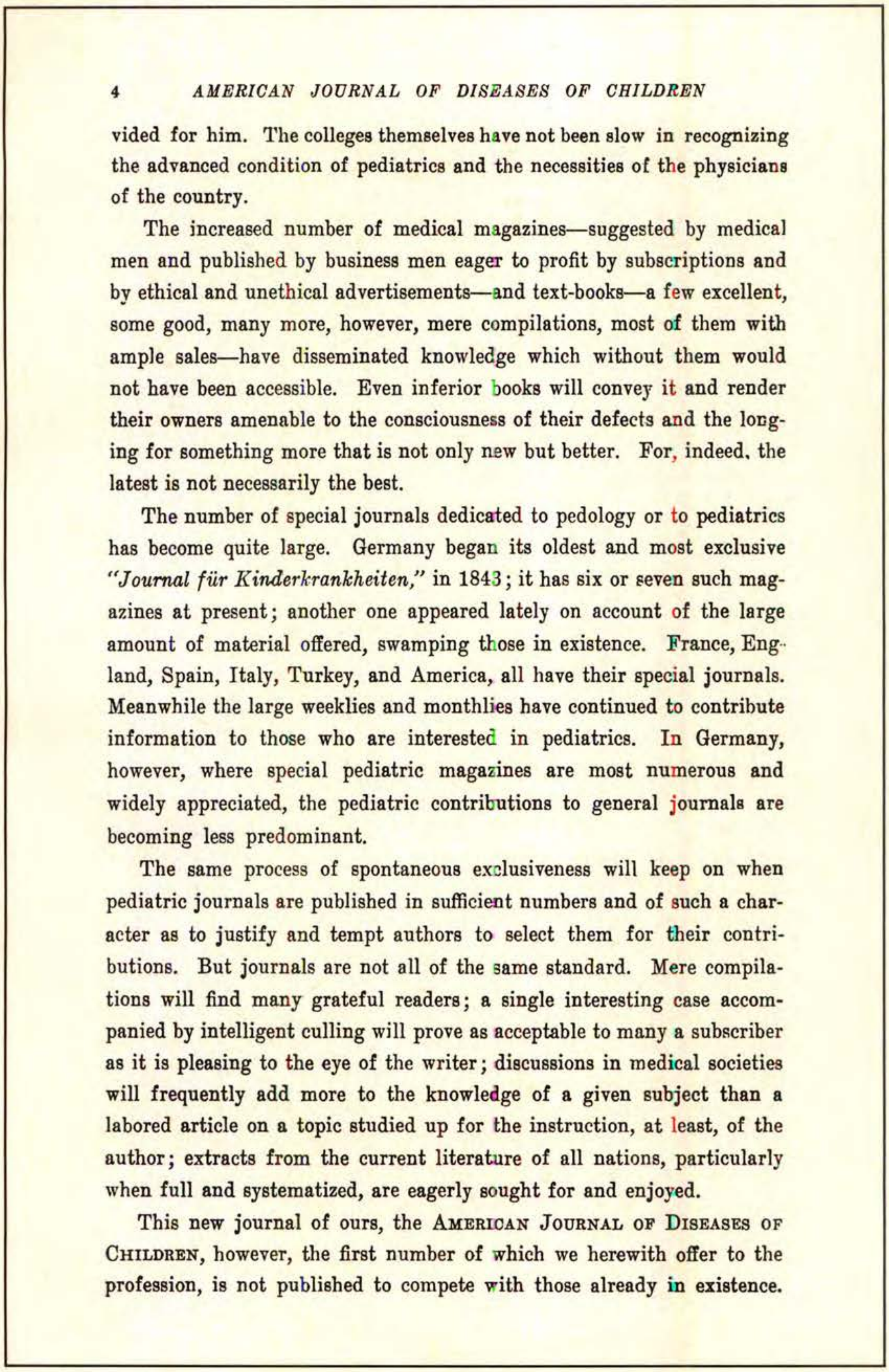


plentiful; our weeklies, monthlies, and quarterlies contained much that was and much that still is of value. The first extensive American papers on diphtheria (1860) and acute rheumatism (1875) were published in magazines. The first volumes of the *American Journal of Obstetrics and the Diseases of Women and Children* (founded in 1869) were almost entirely filled with subjects connected with the anatomy, physiology, and therapeutics of the young. But though the Germans had a special journal since 1843, the first American journal, the *Archives of Pediatrics,* was published by the enthusiastic Watson in 1884 and *Pediatrics* by Dillon Brown in 1896. My readers know that both have rendered good service, both by disseminating knowledge and rousing interest and enthusiasm. At the same time our weeklies have vied with them in supplying the practitioners of the country with information of increasing value.

What all of us have learned is to look on pediatrics not as a specialty, such as ophthalmology or otology, which concern single organs, but as that part of internal medicine and surgery which cannot be measured by the knowledge derived from and applied to the adult; it requires special study and research in order to become both scientific and practical. We learned that there is no uniformity of structure and function in the human organism between conception and death; that childhood must be studied, not from the point of view of reproduction only, but of reproduction *and growth;* that pediatrics does not deal with miniature men and women, with reduced doses and the same class of diseases in smaller bodies, but has its own independent range and horizon, and gives as much to general medicine as it has received from it; that there are anomalies and diseases which are encountered in the infant and child only. On the other hand, there are those which are *mostly* found in children, or with a symptomatology and course peculiar to them; and those, finally, which affect both the young and the old, with such varieties, however, in both symptoms and course, as depend on the size or anatomic structure of the afflicted organ or organism, or the difference in the degree of irritability.[1]

To learn and to teach all that—and many more things—the cooperation of many interests was required. The general practitioner—the majority of whose patients are young—since the belief ceased to be prevalent that the diseases of the small child are "small things," wanted more opportunities to learn than those which his college schooling had pro-

[1] Arch. Pediat., November, 1889.



vided for him. The colleges themselves have not been slow in recognizing the advanced condition of pediatrics and the necessities of the physicians of the country.

The increased number of medical magazines—suggested by medical men and published by business men eager to profit by subscriptions and by ethical and unethical advertisements—and text-books—a few excellent, some good, many more, however, mere compilations, most of them with ample sales—have disseminated knowledge which without them would not have been accessible. Even inferior books will convey it and render their owners amenable to the consciousness of their defects and the longing for something more that is not only new but better. For, indeed, the latest is not necessarily the best.

The number of special journals dedicated to pedology or to pediatrics has become quite large. Germany began its oldest and most exclusive *"Journal für Kinderkrankheiten,"* in 1843; it has six or seven such magazines at present; another one appeared lately on account of the large amount of material offered, swamping those in existence. France, England, Spain, Italy, Turkey, and America, all have their special journals. Meanwhile the large weeklies and monthlies have continued to contribute information to those who are interested in pediatrics. In Germany, however, where special pediatric magazines are most numerous and widely appreciated, the pediatric contributions to general journals are becoming less predominant.

The same process of spontaneous exclusiveness will keep on when pediatric journals are published in sufficient numbers and of such a character as to justify and tempt authors to select them for their contributions. But journals are not all of the same standard. Mere compilations will find many grateful readers; a single interesting case accompanied by intelligent culling will prove as acceptable to many a subscriber as it is pleasing to the eye of the writer; discussions in medical societies will frequently add more to the knowledge of a given subject than a labored article on a topic studied up for the instruction, at least, of the author; extracts from the current literature of all nations, particularly when full and systematized, are eagerly sought for and enjoyed.

This new journal of ours, the AMERICAN JOURNAL OF DISEASES OF CHILDREN, however, the first number of which we herewith offer to the profession, is not published to compete with those already in existence.

For some time it has been noted, however, that the pediatric material offered to *The Journal of the American Medical Association* is rapidly increasing in quantity, and also in the size of the articles. Writers were often annoyed by the delay encountered in the publication of their essays; it has even happened that after a delay of many months, authors of the very highest standing were requested to shorten their articles—in many instances an impossible task. Such occurrences suggested the publication of a new special organ. Even those who insisted on the right of the practitioners of the country—members of the Association—to be amply supplied with pediatric teaching by their own journal, receded from the stand taken by them when convinced by the fact that a new journal would not curtail the printing of pediatric contributions in *The Journal of the American Medical Association* and many others of high standing. On the contrary, with the increasing number of physicians interested and working in the field of pedology, there will be more than merely a vast number of papers; there will be more profundity and research. These our new journal is to gather in, and it is to be the companion and ally of the *Archives of Internal Medicine.* It may rarely give a mere case, still more rarely a prescription; it is to be a receptacle, however, of the very latest in the very best of American and European literatures. But extracts will be few in proportion. Reviews, carefully prepared by competent critics, will be offered from time to time. The bulk of the contents, however, will be original; anatomy—both embryonal and postnatal—physiology, biochemistry, nosology, and therapeutics will come to their own, and will be welcomed as our sources of actual progress. Thus, THE AMERICAN JOURNAL OF DISEASES OF CHILDREN is expected to be one of the number of strictly scientific magazines which, since the first appearance of the *Journal of Experimental Medicine* and its followers, have given American medical journalism its standing as an equal coworker in the modern world of Medicine. *Quod felix faustumque sit.*

A. JACOBI.

CONTENTS OF VOLUME I

JANUARY, 1911. NUMBER 1

PAGE

Introduction. A. Jacobi, M.D., New York 1

Some Anatomic Features of the Child's Thorax and Their Practical Application in Physical Diagnosis. George Fetterolf, M.D., and J. Claxton Gittings, M.D., Philadelphia 6

Observations on Three Hundred Cases of Acute Meningitis in Infants and Young Children. L. Emmett Holt, M.D., New York 26

The Constant Presence of Tubercle Bacilli in the Cerebrospinal Fluid of Tuberculous Meningitis. Josephine Hemenway, M.D., New York. 37

Influenzal Meningitis and its Experimental Production. Martha Wollstein, M.D., New York 42

Amaurotic Family Idiocy. Isaac A. Abt, M.D., Chicago 59

Atypical Scarlet Fever. C. Gilmore Kerley, M.D., New York 70

Progress in Pediatrics 73

FEBRUARY, 1911. NUMBER 2

Congenital Pyloric Stenosis. A. D. Bevan, M.D., Chicago 85

Cerebrospinal Meningitis, its Etiology, Diagnosis, Prognosis and Treatment. Charles Hunter Dunn, M.D., Boston 95

Some Investigations Concerning the Relation Between Carpal Ossification and Physical and Mental Development. Eli Long, M.D., and E. W. Caldwell, M.D., New York 113

Frequency and Significance of Albumin in the Urines of Normal Children. Samuel McClintock Hamill, M.D., Philadelphia, and Kenneth D. Blackfan, M.D., Cambridge, N. Y. 139

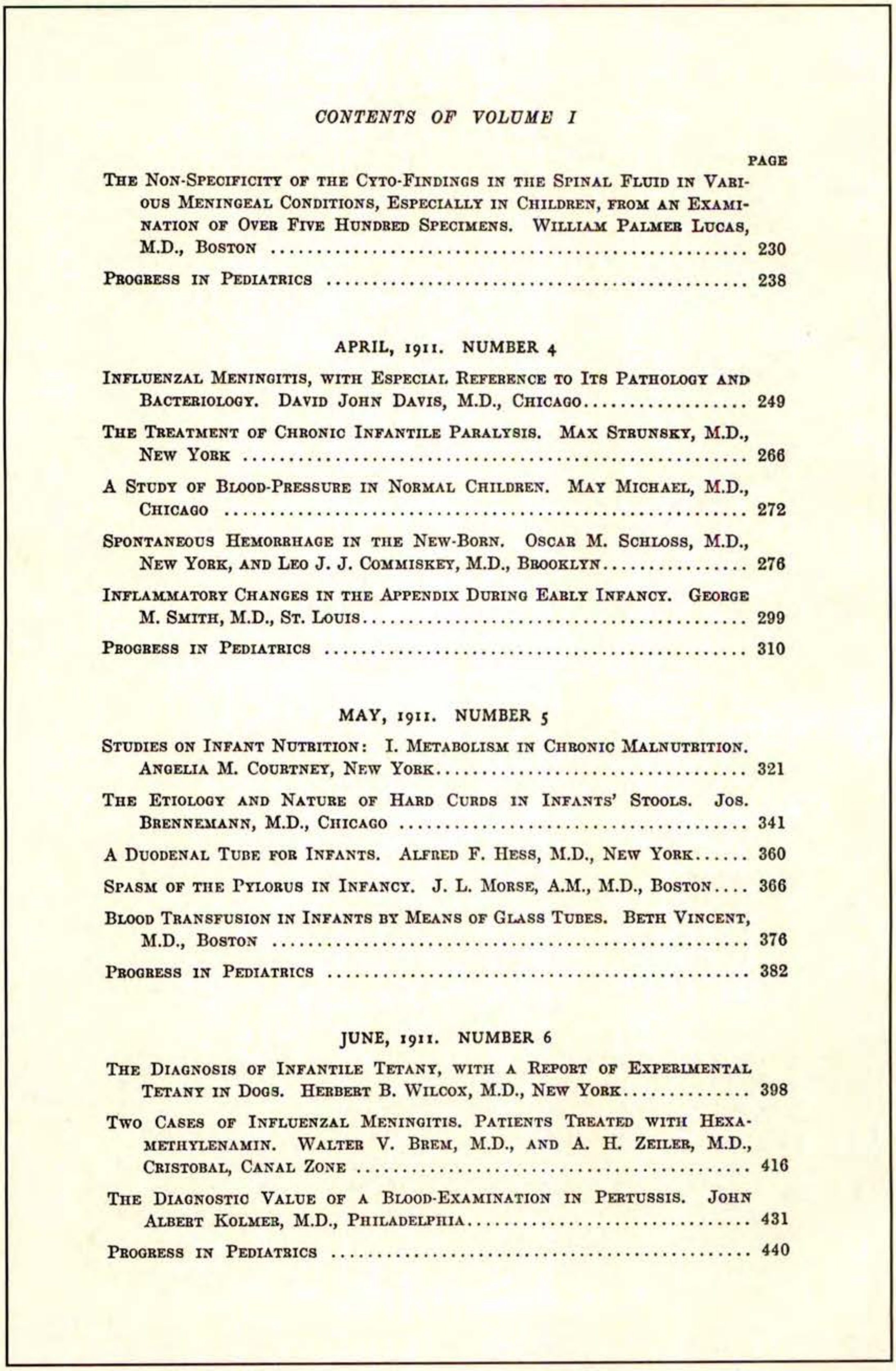
Progress in Pediatrics 164

MARCH, 1911. NUMBER 3

Physiology and Pathology of the Digestion of Fat in Infancy. Fritz B. Talbot, M.D., Boston 173

The Bacteriology of the Blood in Early Life. Frank Spooner Churchill, M.D., and Charles P. Clark, M.D., Chicago 193

The Metabolism of Nitrogen, Phosphorus and the Purin Substances in the New-Born; with Special Reference to the Causation of the Uric Acid Infarcts of the Kidney. Oscar M. Schloss, M.D., New York, and James L. Crawford, M.D., Troy, Texas 203



CONTENTS OF VOLUME I

PAGE

THE NON-SPECIFICITY OF THE CYTO-FINDINGS IN THE SPINAL FLUID IN VARIOUS MENINGEAL CONDITIONS, ESPECIALLY IN CHILDREN, FROM AN EXAMINATION OF OVER FIVE HUNDRED SPECIMENS. WILLIAM PALMER LUCAS, M.D., BOSTON 230

PROGRESS IN PEDIATRICS 238

APRIL, 1911. NUMBER 4

INFLUENZAL MENINGITIS, WITH ESPECIAL REFERENCE TO ITS PATHOLOGY AND BACTERIOLOGY. DAVID JOHN DAVIS, M.D., CHICAGO 249

THE TREATMENT OF CHRONIC INFANTILE PARALYSIS. MAX STRUNSKY, M.D., NEW YORK 266

A STUDY OF BLOOD-PRESSURE IN NORMAL CHILDREN. MAY MICHAEL, M.D., CHICAGO 272

SPONTANEOUS HEMORRHAGE IN THE NEW-BORN. OSCAR M. SCHLOSS, M.D., NEW YORK, AND LEO J. J. COMMISKEY, M.D., BROOKLYN 276

INFLAMMATORY CHANGES IN THE APPENDIX DURING EARLY INFANCY. GEORGE M. SMITH, M.D., ST. LOUIS 299

PROGRESS IN PEDIATRICS 310

MAY, 1911. NUMBER 5

STUDIES ON INFANT NUTRITION: I. METABOLISM IN CHRONIC MALNUTRITION. ANGELIA M. COURTNEY, NEW YORK 321

THE ETIOLOGY AND NATURE OF HARD CURDS IN INFANTS' STOOLS. JOS. BRENNEMANN, M.D., CHICAGO 341

A DUODENAL TUBE FOR INFANTS. ALFRED F. HESS, M.D., NEW YORK 360

SPASM OF THE PYLORUS IN INFANCY. J. L. MORSE, A.M., M.D., BOSTON 366

BLOOD TRANSFUSION IN INFANTS BY MEANS OF GLASS TUBES. BETH VINCENT, M.D., BOSTON 376

PROGRESS IN PEDIATRICS 382

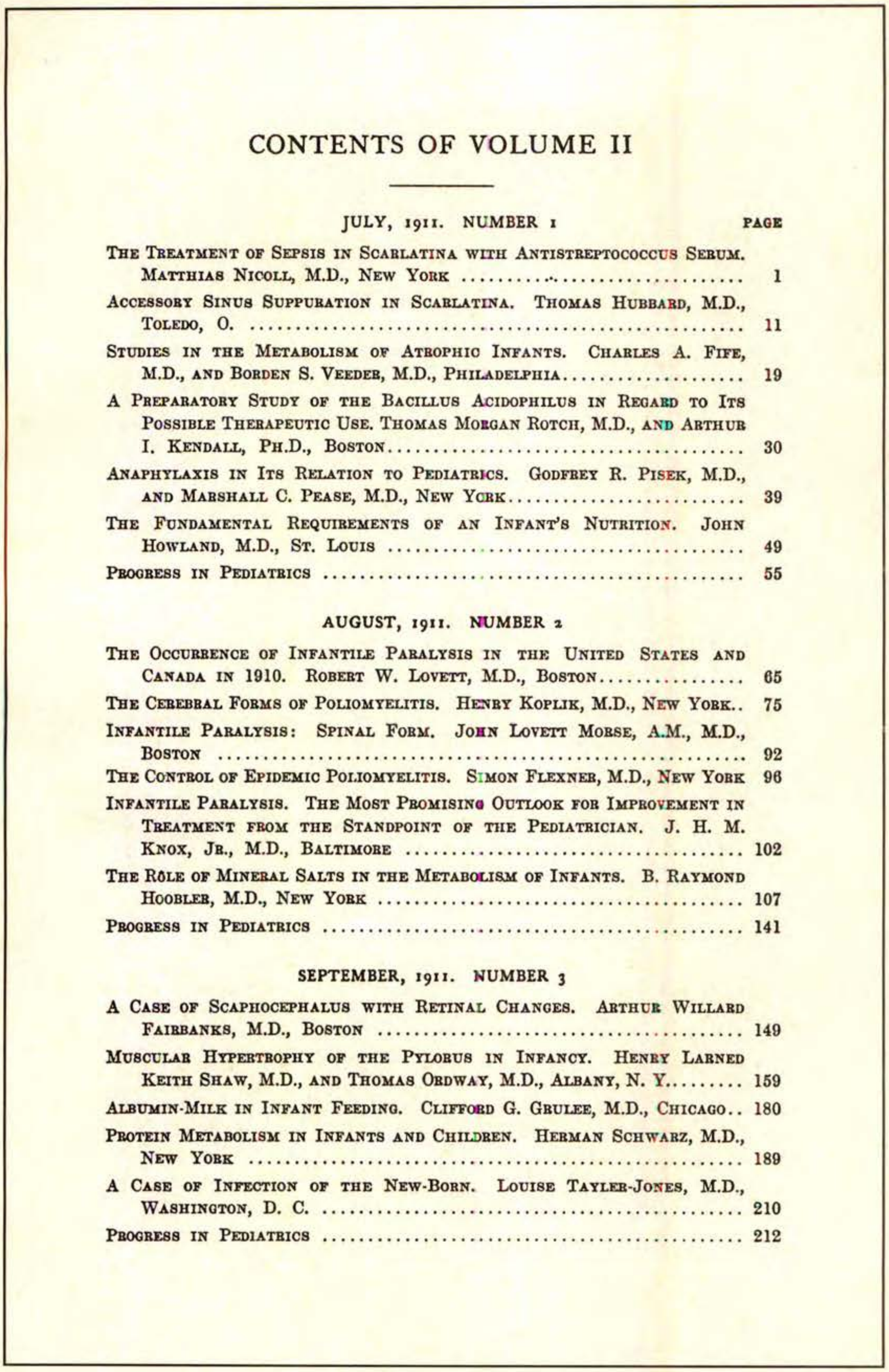
JUNE, 1911. NUMBER 6

THE DIAGNOSIS OF INFANTILE TETANY, WITH A REPORT OF EXPERIMENTAL TETANY IN DOGS. HERBERT B. WILCOX, M.D., NEW YORK 398

TWO CASES OF INFLUENZAL MENINGITIS. PATIENTS TREATED WITH HEXAMETHYLENAMIN. WALTER V. BREM, M.D., AND A. H. ZEILER, M.D., CRISTOBAL, CANAL ZONE 416

THE DIAGNOSTIC VALUE OF A BLOOD-EXAMINATION IN PERTUSSIS. JOHN ALBERT KOLMER, M.D., PHILADELPHIA 431

PROGRESS IN PEDIATRICS 440



CONTENTS OF VOLUME II

JULY, 1911. NUMBER 1

PAGE

THE TREATMENT OF SEPSIS IN SCARLATINA WITH ANTISTREPTOCOCCUS SERUM. MATTHIAS NICOLL, M.D., NEW YORK 1

ACCESSORY SINUS SUPPURATION IN SCARLATINA. THOMAS HUBBARD, M.D., TOLEDO, O. 11

STUDIES IN THE METABOLISM OF ATROPHIC INFANTS. CHARLES A. FIFE, M.D., AND BORDEN S. VEEDER, M.D., PHILADELPHIA.......... 19

A PREPARATORY STUDY OF THE BACILLUS ACIDOPHILUS IN REGARD TO ITS POSSIBLE THERAPEUTIC USE. THOMAS MORGAN ROTCH, M.D., AND ARTHUR I. KENDALL, PH.D., BOSTON.......... 30

ANAPHYLAXIS IN ITS RELATION TO PEDIATRICS. GODFREY R. PISEK, M.D., AND MARSHALL C. PEASE, M.D., NEW YORK.......... 39

THE FUNDAMENTAL REQUIREMENTS OF AN INFANT'S NUTRITION. JOHN HOWLAND, M.D., ST. LOUIS 49

PROGRESS IN PEDIATRICS 55

AUGUST, 1911. NUMBER 2

THE OCCURRENCE OF INFANTILE PARALYSIS IN THE UNITED STATES AND CANADA IN 1910. ROBERT W. LOVETT, M.D., BOSTON.......... 65

THE CEREBRAL FORMS OF POLIOMYELITIS. HENRY KOPLIK, M.D., NEW YORK.. 75

INFANTILE PARALYSIS: SPINAL FORM. JOHN LOVETT MORSE, A.M., M.D., BOSTON 92

THE CONTROL OF EPIDEMIC POLIOMYELITIS. SIMON FLEXNER, M.D., NEW YORK 96

INFANTILE PARALYSIS. THE MOST PROMISING OUTLOOK FOR IMPROVEMENT IN TREATMENT FROM THE STANDPOINT OF THE PEDIATRICIAN. J. H. M. KNOX, JR., M.D., BALTIMORE 102

THE RÔLE OF MINERAL SALTS IN THE METABOLISM OF INFANTS. B. RAYMOND HOOBLER, M.D., NEW YORK 107

PROGRESS IN PEDIATRICS 141

SEPTEMBER, 1911. NUMBER 3

A CASE OF SCAPHOCEPHALUS WITH RETINAL CHANGES. ARTHUR WILLARD FAIRBANKS, M.D., BOSTON 149

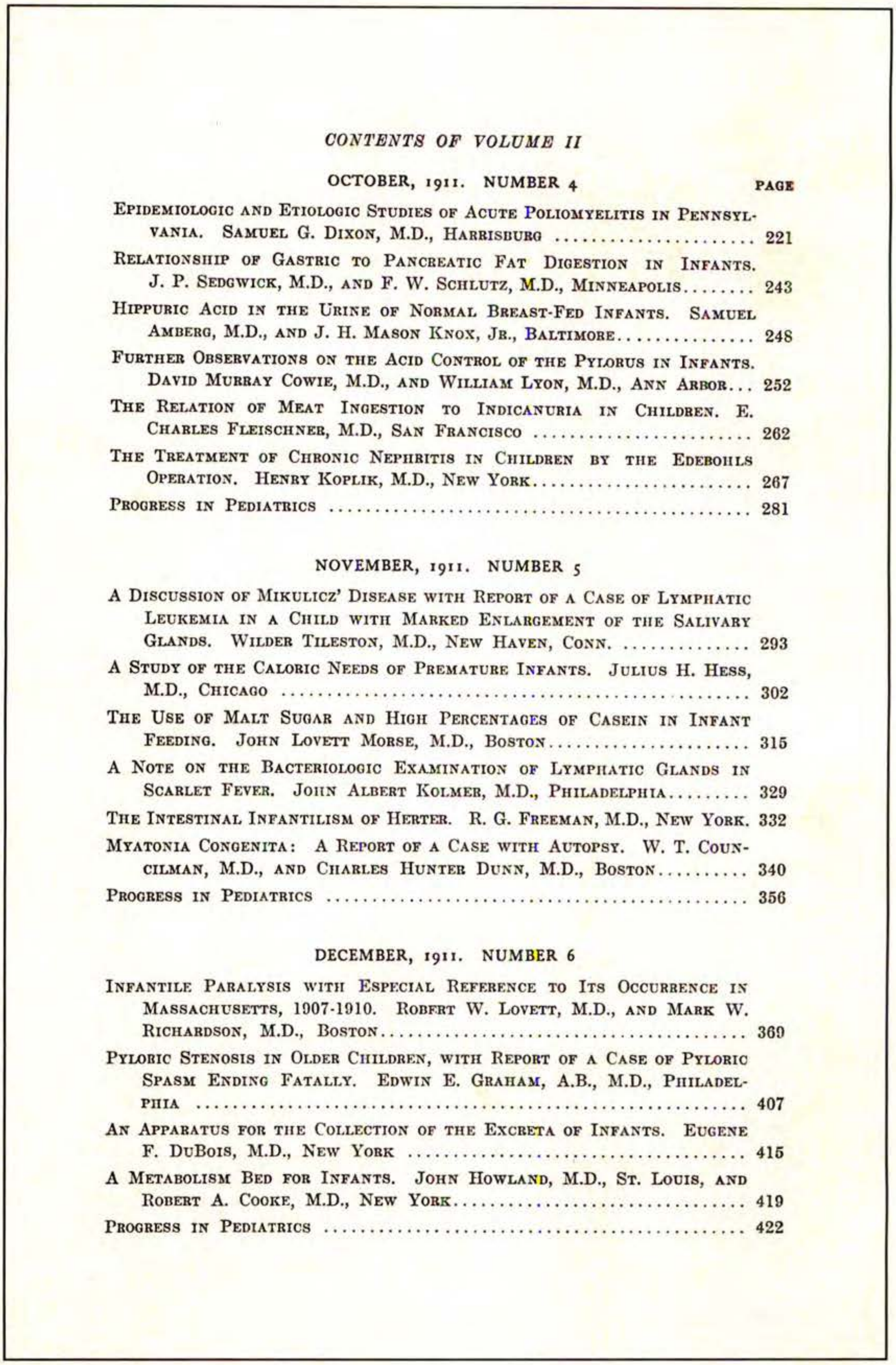
MUSCULAR HYPERTROPHY OF THE PYLORUS IN INFANCY. HENRY LARNED KEITH SHAW, M.D., AND THOMAS ORDWAY, M.D., ALBANY, N. Y.......... 159

ALBUMIN-MILK IN INFANT FEEDING. CLIFFORD G. GRULEE, M.D., CHICAGO.. 180

PROTEIN METABOLISM IN INFANTS AND CHILDREN. HERMAN SCHWARZ, M.D., NEW YORK 189

A CASE OF INFECTION OF THE NEW-BORN. LOUISE TAYLER-JONES, M.D., WASHINGTON, D. C. 210

PROGRESS IN PEDIATRICS 212



CONTENTS OF VOLUME II

OCTOBER, 1911. NUMBER 4

PAGE

EPIDEMIOLOGIC AND ETIOLOGIC STUDIES OF ACUTE POLIOMYELITIS IN PENNSYLVANIA. SAMUEL G. DIXON, M.D., HARRISBURG 221

RELATIONSHIP OF GASTRIC TO PANCREATIC FAT DIGESTION IN INFANTS. J. P. SEDGWICK, M.D., AND F. W. SCHLUTZ, M.D., MINNEAPOLIS........ 243

HIPPURIC ACID IN THE URINE OF NORMAL BREAST-FED INFANTS. SAMUEL AMBERG, M.D., AND J. H. MASON KNOX, JR., BALTIMORE............... 248

FURTHER OBSERVATIONS ON THE ACID CONTROL OF THE PYLORUS IN INFANTS. DAVID MURRAY COWIE, M.D., AND WILLIAM LYON, M.D., ANN ARBOR... 252

THE RELATION OF MEAT INGESTION TO INDICANURIA IN CHILDREN. E. CHARLES FLEISCHNER, M.D., SAN FRANCISCO 262

THE TREATMENT OF CHRONIC NEPHRITIS IN CHILDREN BY THE EDEBOHLS OPERATION. HENRY KOPLIK, M.D., NEW YORK........................ 267

PROGRESS IN PEDIATRICS 281

NOVEMBER, 1911. NUMBER 5

A DISCUSSION OF MIKULICZ' DISEASE WITH REPORT OF A CASE OF LYMPHATIC LEUKEMIA IN A CHILD WITH MARKED ENLARGEMENT OF THE SALIVARY GLANDS. WILDER TILESTON, M.D., NEW HAVEN, CONN. 293

A STUDY OF THE CALORIC NEEDS OF PREMATURE INFANTS. JULIUS H. HESS, M.D., CHICAGO 302

THE USE OF MALT SUGAR AND HIGH PERCENTAGES OF CASEIN IN INFANT FEEDING. JOHN LOVETT MORSE, M.D., BOSTON...................... 315

A NOTE ON THE BACTERIOLOGIC EXAMINATION OF LYMPHATIC GLANDS IN SCARLET FEVER. JOHN ALBERT KOLMER, M.D., PHILADELPHIA......... 329

THE INTESTINAL INFANTILISM OF HERTER. R. G. FREEMAN, M.D., NEW YORK. 332

MYATONIA CONGENITA: A REPORT OF A CASE WITH AUTOPSY. W. T. COUNCILMAN, M.D., AND CHARLES HUNTER DUNN, M.D., BOSTON.......... 340

PROGRESS IN PEDIATRICS 356

DECEMBER, 1911. NUMBER 6

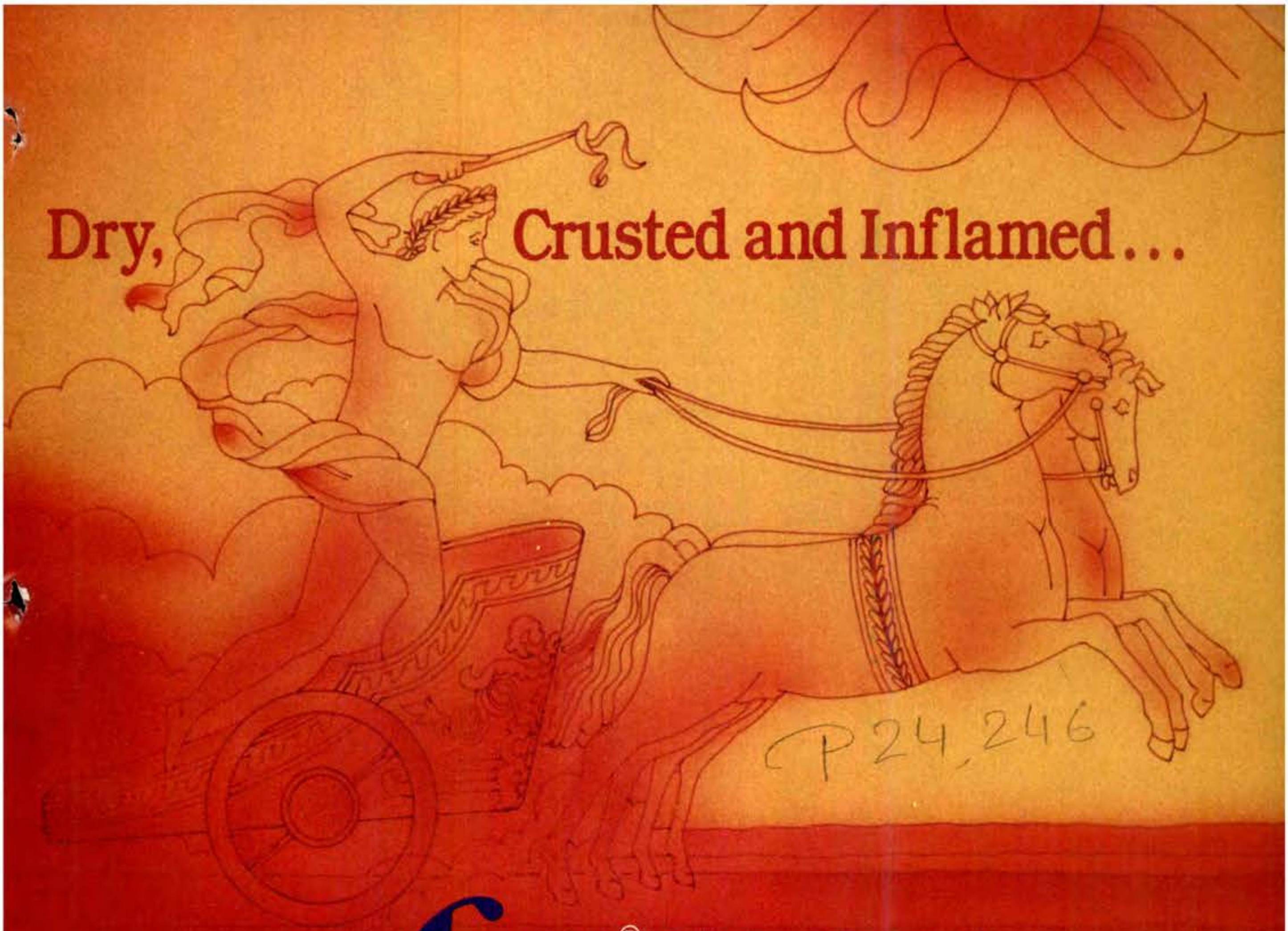
INFANTILE PARALYSIS WITH ESPECIAL REFERENCE TO ITS OCCURRENCE IN MASSACHUSETTS, 1907-1910. ROBERT W. LOVETT, M.D., AND MARK W. RICHARDSON, M.D., BOSTON....................................... 369

PYLORIC STENOSIS IN OLDER CHILDREN, WITH REPORT OF A CASE OF PYLORIC SPASM ENDING FATALLY. EDWIN E. GRAHAM, A.B., M.D., PHILADELPHIA 407

AN APPARATUS FOR THE COLLECTION OF THE EXCRETA OF INFANTS. EUGENE F. DUBOIS, M.D., NEW YORK 415

A METABOLISM BED FOR INFANTS. JOHN HOWLAND, M.D., ST. LOUIS, AND ROBERT A. COOKE, M.D., NEW YORK................................ 419

PROGRESS IN PEDIATRICS 422



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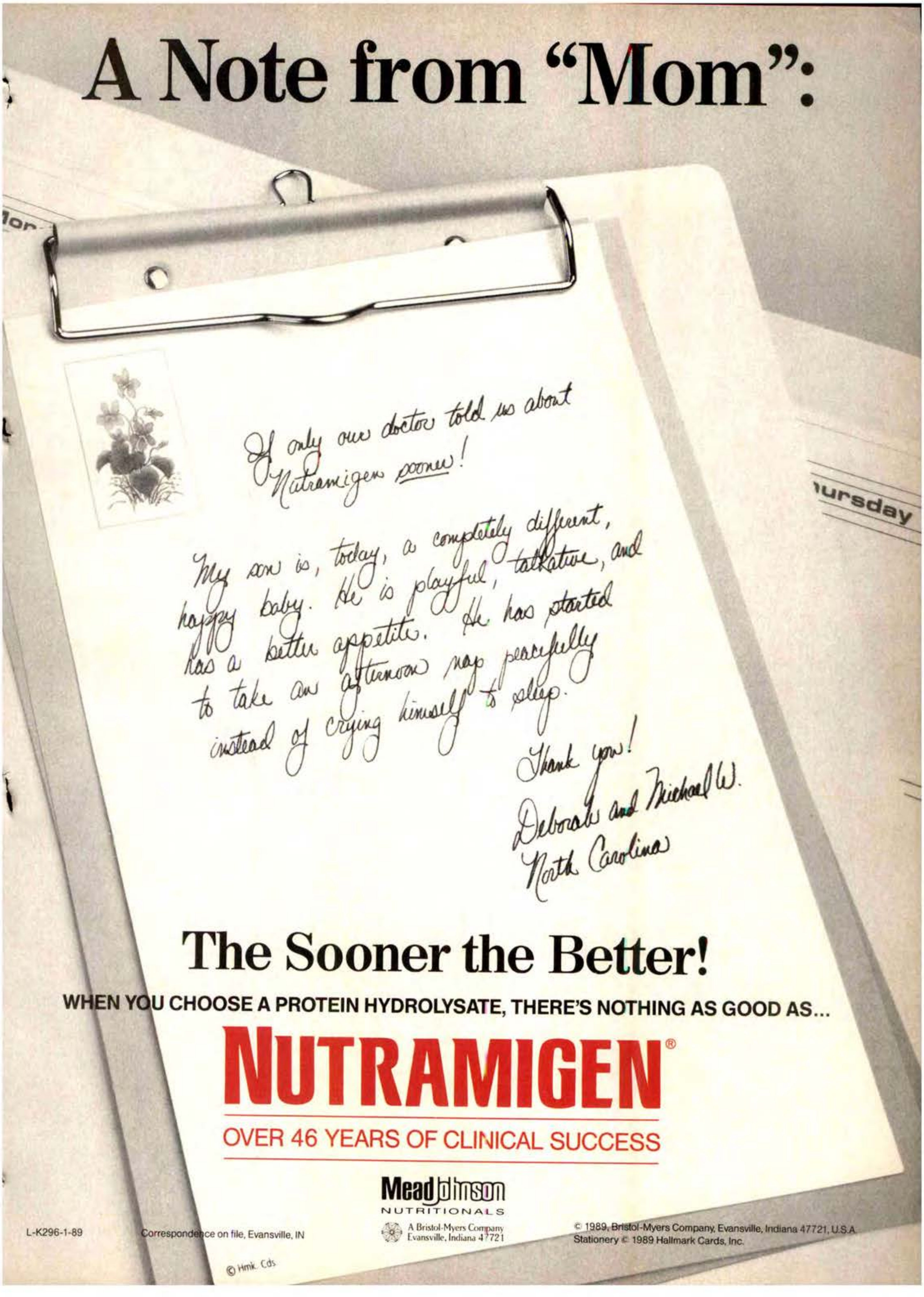

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The Pediatric Forum

This department of AJDC *is reserved for comment, criticism, observation, and discussion of "issues of current concern and importance for children's health." The Editor encourages our readers to express themselves on a variety of topics and issues. Further, we encourage the submission of unique and brief clinical and scientific observations that do not fulfill the criteria for original articles.*

1991 Annual Meeting

The annual meeting of The American Pediatric Society, The Society for Pediatric Research, and The Ambulatory Pediatric Association will be held April 29 through May 2, 1991, at the New Orleans (La) Hilton and Rivergate Convention Center. For further information, contact the APS/SPR Association Headquarters, 2650 Yale Blvd SE, Suite 104, Albuquerque, NM 87106; (505) 764-9099; FAX (505) 842-8227; or the Ambulatory Pediatric Association, 6728 Old McLean Village, McLean, VA 22101; (703) 556-9222.

Characteristics of Perinatal Cocaine-Exposed Infants With Necrotizing Enterocolitis

Sir.—Recently, attention has been directed at the complications related to cocaine use during pregnancy, including placental abruption, spontaneous abortion, intrauterine growth retardation, and premature labor and delivery.[1,2] Neonatal complications have also been noted, including neurobehavioral disturbances, microcephaly, intrauterine cerebrovascular accidents, and possibly malformations secondary to vascular disruptions.[3-5] Previous reports have suggested that intrauterine cocaine exposure may also be associated with neonatal necrotizing enterocolitis (NEC).[6,7] We report a retrospective review of the relationship between perinatal cocaine exposure and the development of NEC in the newborn period.

Patients and Methods.—All admissions to the neonatal intensive care unit (NICU) at a medical center that provides care to an urban indigent population were reviewed from July 1987 through June 1989. Infants with perinatal cocaine exposure who developed NEC during this period were compared with nonexposed infants. Infants were designated to have had perinatal cocaine exposure if (1) maternal urine drug screens performed with the mother's consent in the prenatal clinic or at the time of delivery were positive, or (2) newborn urine drug screens indicated cocaine metabolites at the time of admission to the NICU. During this period, maternal and newborn urine toxicologic studies were ordered at the discretion of the attending physician. Maternal and newborn screening was performed if there was a history of maternal drug use or compatible life-style, or if the newborn had unexplained neurologic (lethargy, jitteriness, agitation, or hypertonicity) or respiratory (tachypnea or nasal stuffiness) symptoms within the first 48 hours of life. Urinary excretion of ecgonine and benzoylecgonine was detected by enzyme modified immunoassay technique with confirmation by gas chromatography.

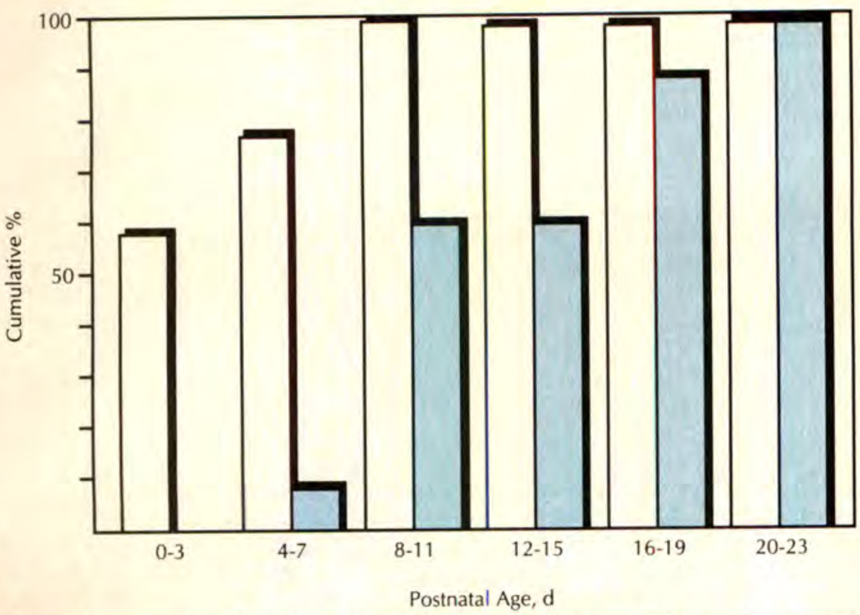
Infants were designated as having definite NEC if they had signs, symptoms, and roentgenographic findings consistent with those of stage IIA or greater of the modified Bell's criteria.[8] All infants included in this report had abdominal distention, bloody stools, and pneumatosis intestinalis roentgenographically. We compared descriptive characteristics (Apgar scores, umbilical cord blood gases, and gestational age), clinical course, and intrauterine growth variables between infants with and without cocaine exposure who developed NEC. We also compared risk factors and complications associated with NEC between groups.

During the 2-year period, there were 5937 live births and 794 admissions to the NICU. Of the NICU patients who underwent drug testing, cocaine metabolites were seen in 69 (8.7%). The overall incidence of NEC (stage IIA or greater) was 3.3% (26 of 794). Thirty-eight percent (10 of 26) of the infants with NEC had documentation of antenatal or intrapartum cocaine exposure. All infants had a positive screen result prior to the onset of NEC. Other drugs identified included cannabinoids (in one case) and opiate derivatives and alcohol (in one case). None of the other 16 infants with NEC had a maternal history of drug use; three of these were tested and had negative urine drug screen results.

Infants with NEC were grouped and compared according to perinatal cocaine exposure. Cocaine-exposed infants had significantly greater gestational age than nonexposed infants (31.2±3.5 weeks vs 27.3±2.4 weeks; $P<.01$); however, there were no significant differences in birth weight (1490±646 g vs 1098±817 g). Thirty percent (3 of 10) of the cocaine-exposed infants had a weight less than the 10th percentile for gestational age. There were no extremely-low-birth-weight (less than 800 g) infants in the cocaine-exposed group, while 44% (7/16) of the nonexposed group had low birth weights ($P=.03$). No differences existed in gender or route of delivery. Two patients in the cocaine-exposed group were term infants admitted to the well-baby nursery with no known risk factors for NEC. In addition to those infants with NEC, two other cocaine-exposed infants had multiple atretic areas of the small intestine.

Cocaine-exposed infants developed symptoms of NEC at a younger postnatal age than the nonexposed group (Figure). Three of the cocaine-exposed infants had not had feedings prior to the onset of NEC symptoms. Selected risk factors[8] for the development of NEC were compared between the cocaine-exposed and nonexposed groups (Table). There were significantly more infants in the nonexposed group with one or more risk factors associated with NEC. There were no significant differences in the incidence of positive blood or cerebrospinal fluid cultures between groups. The cases of NEC occurred sporadically during the period reviewed and no clusters of cases were noted. Complications attributed to NEC including perforation, stricture, and need for surgical intervention were not different between groups. There were two deaths in the cocaine-exposed group and three in the nonexposed group.

Comment.—Perinatal complications that predispose to development of NEC include prematurity, respiratory distress syndrome, low birth weight, asphyxia, and arterial occlusion associated with umbilical artery catheters.[8] As would be expected, these factors were frequently identified among the group of infants with NEC who did not have cocaine exposure. Infants with NEC who had intrauterine cocaine exposure were less likely to have known antecedent risk factors. Two infants in the cocaine group were low-risk infants born at term, who did not have prior feeding. None of the cocaine-exposed infants born at term had colonization with infectious organisms that might have predis-



Cumulative percentage of infants developing NEC during first 23 days of life grouped according to cocaine exposure. Mean age at onset of NEC symptoms was significantly younger for the cocaine-exposed group ($P<.001$). Open bars represent the cocaine-exposed group (mean age, 4.5 ± 2.9 days), and tinted bars, the nonexposed group (mean age, 13.8 ± 6.8 days).

Selected Risk Factors for Necrotizing Enterocolitis

	Cocaine-Exposed (n = 10)	Non-exposed (n = 16)
Respiratory distress syndrome	4	8
5-minute Apgar <8	2	8*
Cord pH <7.20	2	7
Preterm (<37 wk)	7	15
Umbilical vessel catheters	3	10
Polycythemia (hematocrit ≥0.65)	1	2
≥1 risk factor	3	13*

*$P<.01$.

posed to development of NEC.

Previous reports have indicated that perinatal cocaine use may cause ischemic injuries of the fetus and newborn—particularly cerebrovascular accidents and cerebral leukomalacia.[9,10] Necrotizing enterocolitis in cocaine-exposed infants who otherwise have no known risk factors suggests that fetal cocaine exposure may cause gastrointestinal ischemic injury. Early onset of NEC symptoms in the cocaine-exposed infants provides additional evidence that the injury was the result of an antenatal event. Intestinal atresia, which may also be the result of vascular insufficiency, was diagnosed in two additional cocaine-exposed infants, further documenting this reported association.[5,7]

There are several possible mechanisms for cocaine-induced gastrointestinal ischemia. Maternal hemodynamic responses include reduced uterine blood flow via vasoconstriction resulting in fetal hypoxemia, tachycardia, and hypertension.[11-13] Chronic placental insufficiency may result in intrauterine fetal growth retardation and/or altered circulation to nonvital organs, including the gastrointestinal tract. Diminished splanchnic circulation may also occur as a consequence of decreased cardiac output in the newborn, recently associated with perinatal cocaine use.[14] In addition, after maternal administration, cocaine may cross the placenta[11] and directly lead to fetal vasoconstriction possibly by a calcium-regulated mechanism.[15]

Our study is limited in interpretation because we only performed urine testing in mothers or infants based on history or clinical suspicion. We identified apparently low-risk infants who developed NEC following perinatal cocaine exposure; however, because we did not test universally, we may have misclassified some of the "nonexposed" infants. Additionally, multiple drug use is common and unrecognized agents may have been responsible for or had additive effects in predisposing to NEC in these infants. However, only two infants with NEC were identified who had excretion of drugs or metabolites other than cocaine.

We suggest that perinatal cocaine exposure be considered a risk factor for the development of NEC in infants. Accordingly, awareness of this association may lead to altered interpretation of feeding difficulties and related symptoms in cocaine-exposed newborns.

GREGORY J. DOWNING, DO
STANLEY R. HORNER, DO
HOWARD W. KILBRIDE, MD
Children's Mercy Hospital
University of Missouri–Kansas City
School of Medicine
2401 Gillham Rd
Kansas City, MO 64108-9898

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Current Social Practices Leading to Water Intoxication in Infants

Sir.—We recently treated three children with water intoxication who were receiving evaporated milk formula. During that same period (1985 to 1989), there were 14 instances of admissions to our institution for water intoxication, which we have already noted as having become more frequent than in the recent past.[1] Ordinarily, one would expect infants receiving evaporated milk formulas to be vulnerable to hypernatremia.[2] We tried to find a reason for this unexpected outcome.

In each instance, the problem was related to improper feeding practices. The mothers, all of whom were participants in the Women, Infants, Children (WIC) program at our institution, were either excessively diluting the milk or using small amounts of properly reconstituted evaporated milk to supplement larger quantities of relatively electrolyte-free fluids such as diluted fruit juices or water.

The parents of the infants enrolled in the WIC program are carefully instructed in the proper use of the conventional infant formulas for which they are issued redemption coupons. They receive four coupons weekly each month on which the name of a commonly used commercial infant formula is clearly written.

We investigated the circumstances of intoxication, since the frequency of water intoxication exceeded our prior experience and, given the usual feeding practices in the community, should not have occurred.

Subjects and Methods.—In the winter of 1988/1989, three patients receiving evaporated milk were admitted to the hospital with convulsions. Each had histories of feeding that revealed excessive water intake.

Patient 1 was age 4 months and had been admitted for seizures and diarrhea. Chemical analyses of serum revealed the following values: sodium, 128 mmol/L; potassium, 5 mmol/L; chloride, 105 mmol/L; bicarbonate, 9 mmol/L; glucose, 8.2 mmol/L; and urea nitrogen, 1.4 mmol/L. His recent daily food intake consisted of 7 oz of evaporated milk (two parts water and one part evaporated milk) every 3 to 4 hours, 16 oz of juice, and 8 oz of water.

Patient 2 was age 10 months and had been admitted for seizures. Chemical analyses of serum revealed the following values: sodium, 115 mmol/L; potassium, 4.1 mmol/L; chloride, 90 mmol/L; bicarbonate, 10 mmol/L; glucose, 7.2 mmol/L; and urea nitrogen, 3.9 mmol/L. His food intake consisted of more than 20 oz of evaporated milk (diluted with an equal part of water) 16 oz of water, 8 oz of grape juice diluted with water, and table food.

Patient 3 was age 6 months and had been admitted for seizures. Chemical analyses of serum revealed the following values: sodium, 113 mmol/L; potassium, 5.0 mmol/L; chloride, 86 mmol/L; bicarbonate, 13 mmol/L; glucose, 8.2 mmol/L; and urea nitrogen, 3.2 mmol/L. His food intake consisted of 6 oz of evaporated milk (diluted with an equal part of water) every 4 hours, 4 oz of juice, strained vegetables and fruit, and 6 oz of water. (Dietary history was unreliable because there were multiple caretakers that day.)

In all three patients, the sodium level in the serum returned to normal within 36 hours after restricted fluid intake and was sustained at that level when ordinary feedings were reinstated.

Comment.—Water intoxication occurs when water without solute is given rapidly. This appears to have been the case for these three patients. Even with a vague feeding history, one must conclude that a sodium level of 113 mmol/L in serum in a previously healthy child must have been the end result of the ingestion of large quantities of solute-poor liquid. One may calculate that patient 3, who previously was well, weighed 5.91 kg, and had a sodium level of 113 mmol/L and convulsions must have ingested 700 to1000 mL of water in a brief period of time to have brought the sodium level down to that level.

As early as 1923, investigators have referred to the complex of neurologic symptoms and signs resulting from the rapid decrease in the osmolality of extracellular fluid as water intoxication.[3]

The convulsions in water intoxicated infants are a manifestation of a rapid drop in extracellular solute concentration causing osmolal equilibration with the central nervous system to be achieved by movement of water from plasma to cerebrospinal fluid and neurons. The dominant solute of extracellular fluid, sodium and chloride ions, crosses the brain capillaries more slowly than water molecules because the endothelial cells of these capillaries (unlike most others) form a barrier layer from the tight junctions between adjacent cells.[4] The diffusion of water along an osmolal gradient causes brain swelling, which produces water intoxication and its symptoms.

We tried to find the causes of water intoxication in our patients. The nutrition educators of the WIC program at our hospital provided the appropriate information and described correct infant feedings. There appear to be several concomitant factors that set the stage for improper feeding. Many of our patients' families have emigrated from Caribbean countries where evaporated milk is commonly used in the kitchen, such as in coffee and cooking. It became apparent that a number of food store operators within the community are exchanging WIC coupons designated for conventional infant formula for the much less expensive evaporated milk. As an incentive for the consumer, the vendor includes more merchandise (eg, more cans of evaporated milk or extra groceries). In our experience, however, this exchange is not equal to the real value of the infant formula, thus creating a profit margin for the vendor.

The patient, having received the evaporated milk directly from the vendor, has not been educated by health care providers on the proper use of this product nor on the proper balance of milk, nonmilk fluids, and other infant foods.

Conclusions.—Clinicians should be aware that convulsions related to water intoxication may be direct results of corruption of the WIC infant feeding program, leading to a perversion of infant feeding practices by inexperienced and unsophisticated care givers, themselves meaning well.

ANNABELLE V. SCHAEFFER, MD
STUART DITCHEK, MD
Children's Medical Center of Brooklyn
Health Science Center
450 Clarkson Ave, Box 49
Brooklyn, NY 11203-2098

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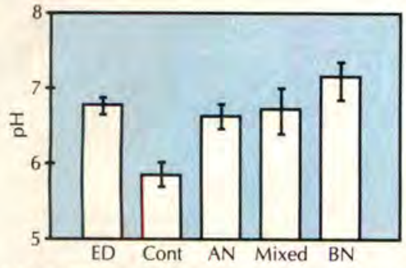
Alkaline Urine Is Associated With Eating Disorders

Sir.—Alkaline urine has traditionally been associated with *Proteus* urinary tract infections.[1] In the absence of an infection, clinical findings might suggest other diagnoses, but these are rare in adolescents. The following are some of the traditional causes of alkaline urine[2]: (1) urinary tract infection (*Proteus* and others); (2) metabolic alkalosis (pyloric stenosis and others); (3) failure of acidification (renal tubular acidosis, chronic renal failure, or aldosterone abnormalities); (4) ingestion (salicylate, sodium bicarbonate, acetazolamide, etc); and (5) respiratory alkalosis (hyperventilation).

After noticing alkaline urine in a number of otherwise healthy patients with eating disorders, we prospectively examined urine pH in a hospital-based adolescent medicine practice to determine



Urine pH (mean ± SE) in outpatients presenting to the adolescent medicine division. The difference between control subjects and patients with eating disorders was highly significant, at $P<.001$. ED indicates patients with eating disorders (n = 46); Cont, control subjects (n = 28); AN, patients with anorexia nervosa (n = 28); Mixed, mixed patients with (nonspecific) eating disorders (n = 9); and BN, patients with bulimia nervosa (n = 9).

if elevated urine pH is associated with eating disorders.

Patients and Methods.—All female patients presenting to a suburban New York adolescent medicine outpatient division during a 5-week period were asked to participate in this study of urine pH. Informed consent was obtained, and subjects were classified as patients with eating disorders (n = 46) or control subjects (n = 28) by their physicians according to the criteria given by the *Diagnostic and Statistical Manual of Mental Disorders–Revised Third Edition* for the diagnoses of anorexia nervosa (without self-induced vomiting), bulimia nervosa, and nonspecific (mixed) eating disorders.[3] Patients recovering from eating disorders were included, even if they no longer met the strict criteria (ie, percentage of weight lost or frequency of vomiting) for their diagnosis at the time of the study.

The control subjects presented for a variety of reasons, including general and gynecologic health maintenance, acute illness (such as viral syndrome), and emergency room or inpatient follow-up. Patients with urinary tract infections or renal disease were excluded (n = 2). None of the patients in either group had any of the known causes of alkaline urine listed above, and none was hypertensive or showed signs of adrenal dysfunction.

Patients with eating disorders completed a questionnaire about the frequency and duration of eating and purging behaviors before examination. Although they were told that this information would be used only for the study and would not affect their treatment, it is possible that the responses of some patients were not accurate. Physicians recorded clinical data at the time of the visit. Urinalysis was performed by a physician or nurse on freshly voided specimens, using the multitest reagent strips for urinalysis (Ames Labstix dipstick). These individuals were not blinded, but in all cases the result of the dipstick test was easily determined, so bias was not likely to have occurred. All samples were obtained on weekday afternoons during the summer of 1988.

Distribution of Alkaline Urine by Diagnosis*

	Urine pH Value, No.	
	≤7	>7
Patients with eating disorders	29	17
Control subjects	27	1

*$P = .001$ by χ^2 analysis. Specificity was 96%; sensitivity, 37%; and positive predictive value, 94%.

Statistical analysis was performed using the Mann-Whitney rank sum test, χ^2 analysis, or Spearman's correlation method, as appropriate. Bonferroni's adjustment was used to correct for multiple comparisons.

Results.—The urine pH of patients with eating disorders (mean ± SD, 6.8 ± 0.8) was significantly higher than that of control patients (5.9 ± 0.8; $P<.001$). This difference remained when patients were classified by specific diagnosis (Figure), but there were no significant differences among the diagnostic groups.

Alkaline urine, defined as urine with a pH value over 7, was found significantly more often in patients with eating disorders ($P = .001$) (Table). Seventeen of 46 patients with eating disorders had alkaline urine, while only one of 28 controls did. The specificity of alkaline urine for eating disorders was 96%, but sensitivity was only 37%. In our population, with a large number of patients with eating disorders (58% of female patient visits), the positive predictive value of alkaline urine for eating disorders was 94%.

Using χ^2 analysis, a number of clinical variables were examined for association with alkaline urine. Patients who weighed less than 85% of ideal body weight were significantly more likely to have alkaline urine ($P<.05$). Patients who reported vomiting within the previous month were also more likely to have alkaline urine ($P<.05$), but there was no association with reports of vomiting in the preceding week or distant past.

There was no association between the presence of alkaline urine and a number of other clinical variables, including change in weight during the previous week or month; urine ketones, protein, or specific gravity; duration of disease or amenorrhea; or self-report of the use of diuretics, laxatives, or salt. The patient's perception of the success of treatment was not associated with high urine pH, and there was also no association between urine pH and blood pressure.

In longitudinal examination of three patients individually, no correlation was found between weight and urine pH in a series of 10 to 30 weekly visits.

Comment.—Eating disorders are not traditionally included in the differential diagnosis of alkaline urine. This study demonstrates that alkaline urine is found in a substantial number of adolescents with eating disorders, while it is almost never found in those with other diagnoses. In our suburban adolescent patient population, in whom eating disorders are much more common than *Proteus* urinary tract infections, renal or adrenal diseases, or acute ingestions, the most likely diagnosis in a patient with alkaline urine is an eating disorder. Using the simple dipstick method, no special laboratory equipment was required to detect alkaline urine in our patients.

The presence of alkaline urine is not used in our adolescent medicine practice to make the diagnosis of an eating disorder; we rely on our experience with these conditions and consultation with psychologists, social workers, and nutritionists. However, the general pediatrician who rarely sees patients with eating disorders may use alkaline urine as a "flag" to signify the possibility of an eating disorder or to supplement clinical impressions. While the low sensitivity of the urine dipstick pH test for eating disorders precludes its use in ruling out the diagnosis, it may prove useful as a quick and inexpensive marker for the presence of these disorders in the clinician's office.

Elevation of urine pH was seen in all types of eating disorders, but was most common in two groups: the self-described vomiters and the most malnourished patients. Self-induced vomiting has been associated with alkaline urine in previous reports[4] due primarily to loss of acid in the vomitus. It is possible that elevated urine pH levels may be a marker for surreptitious vomiting, but other abnormalities in patients with eating disorders, listed below, may also cause alterations of net acid balance that increase urine pH levels: (1) self-induced vomiting (gastrointestinal acid loss)[4]; (2) "alkaline tide" (caused by release of bicarbonate into the gastric venous drainage after large meals are eaten in anticipation of weigh-in)[5]; (3) diet low in meat, high in vegetables, citrus fruits, and dairy products (decreased acid metabolites from meat[6] with increased organic acids and calcium salts[7] lead to abnormal net alkali balance); (4) osteoporosis (release of hydroxyapatite, a basic compound, during demineralization[8] from estrogen deficiency); and (5) hypochloremic alkalosis (from hyperaldosteronism or contraction alkalosis,[9] due to diuretic or laxative abuse).

Most likely, several of these mechanisms occur in patients with eating disorders, and because more than one mechanism may be present in a single patient, it is difficult to assess an individual's progress using urine alkalinity as a marker. Further study of patients with eating disorders under more controlled inpatient settings, in which the numerous variables that may contribute to the formation of alkaline urine can be monitored, is necessary to determine which factors are most important. Nonetheless, the finding of alkaline urine in an adolescent is significant and should always be investigated.

Martha R. Arden, MD
Lauren Budow, MD
Douglas W. Bunnell, PhD
Michael P. Nussbaum, MD
I. Ronald Shenker, MD
Marc S. Jacobson, MD
Division of Adolescent Medicine
Schneider Children's Hospital
Long Island Jewish Medical Center
Albert Einstein College of Medicine
New Hyde Park, NY 11042

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Major Congenital Neurologic Malformations

Sir.—I applaud the attempt by Wiswell et al[1] to estimate the current incidence of major congenital neurologic malformations. One factor may have caused an underestimate of the reported incidence. Many military posts are located in remote locations. When these malformations are discovered in utero, the mother is usually given the option of delivering in the nearest civilian institution with appropriate treatment capabilities or traveling a long distance to a major military medical center. Often, travel to the military facility is very inconvenient and requires a separation of the family. Many mothers elect to deliver in a civilian hospital. These patients are apparently not accounted for in the study, since it only contains infants born in US Army hospitals. The true current incidence of these malformations is probably higher then estimated in the study.

CPT Brian D. Ryals, MC, USA
Department of Child Neurology
Walter Reed Army Medical Center
Washington, DC 20307

1. Wiswell TE, Tuttle DJ, Northam RS, Simonds GR. Major congenital neurologic malformations: a 17-year study. *AJDC.* 1990;144:61-72.

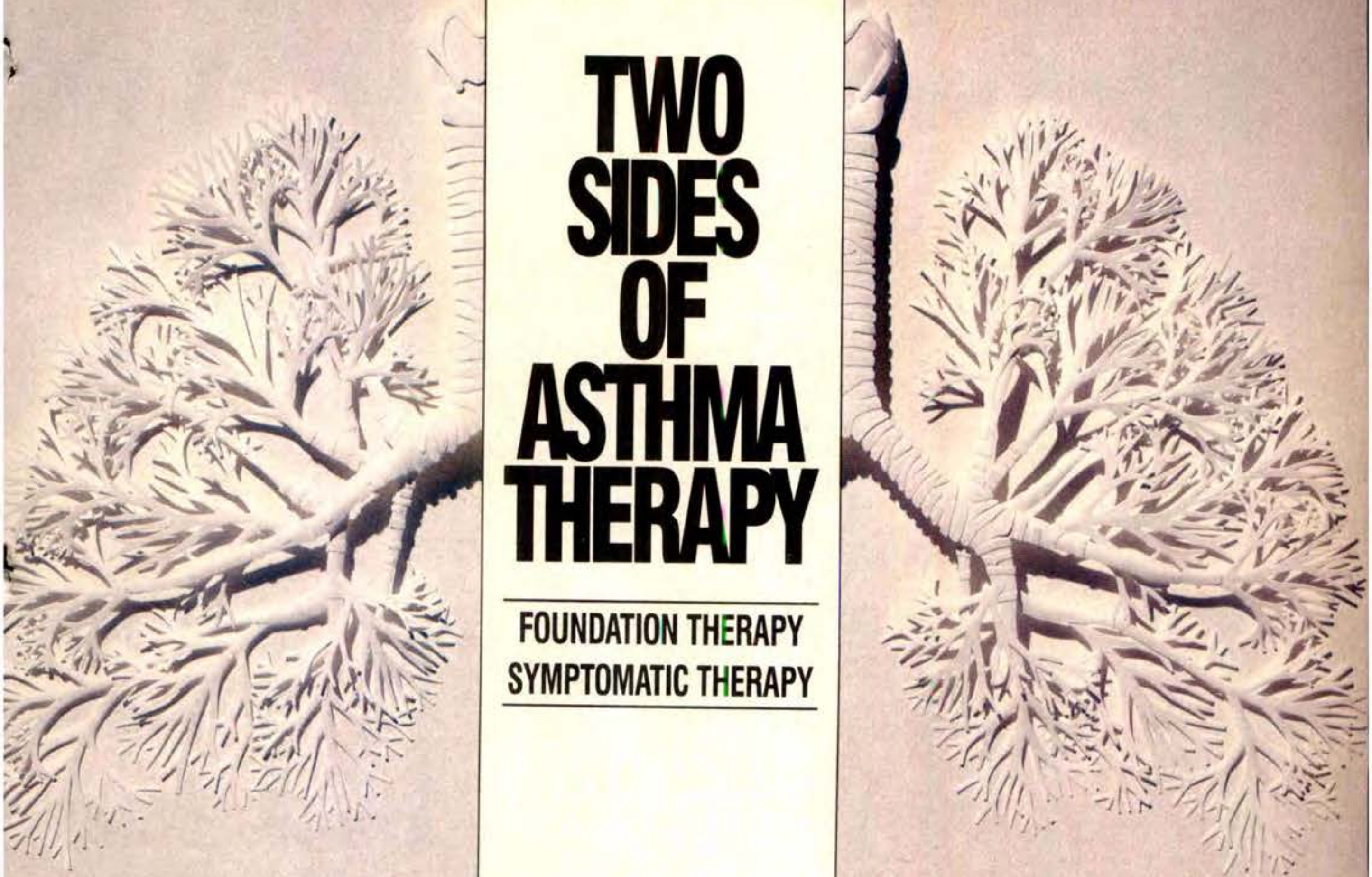
In Reply.—I appreciate Dr Ryals' comments regarding the incidence of major congenital neurologic malformations that we recently reported.

Having spent many years as a military physician, I recognize that pregnant women known to be carrying fetuses with malformations are not infrequently referred to civilian hospitals. However, this has likely played a minimal role in affecting the results of our study. Only in the past 2 years has routine α-fetoprotein screening been performed on all pregnant woman in the major army medical centers, a period subsequent to the dates of the study. In addition, most of the smaller military hospitals do not have this capability. Furthermore, ultrasound study is not routinely performed on pregnant women. Although they have been commonly performed since the mid-1980s, the minority of women undergo ultrasound studies.

α-Fetoprotein levels in amniotic fluid have been evaluated since the mid-1970s. However, these evaluations were performed only in women with prior histories of having a child with a neural tube defect. Fewer than 5% of all infants with neural tube defects have siblings with the same defect. Thus, during the period of the study, the vast majority of women who delivered babies with such defects were unlikely to have undergone such screening.

We suspect that the incidence of neural tube defects from 1971 to 1987 was minimally affected by prenatal diagnosis and referral to civilian hospitals for either abortion or delivery. It is noteworthy that many investigators in Great Britain have found the enormous decline in the occurrence of these malformations during the past two decades more likely to have been influenced by unknown factors than by prenatal screening.

Thomas E. Wiswell, MD
Neonatology Service
Department of Pediatrics
Walter Reed Army Medical Center
Washington, DC 20307-5001



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DESCRIPTION: INTAL Inhaler (cromolyn sodium inhalation aerosol) is a metered dose aerosol unit for oral inhalation containing micronized cromolyn sodium, sorbitan trioleate with dichlorotetrafluoroethane and dichlorodifluoromethane as propellants. Each metered spray delivers to the patient approximately 800 mcg of cromolyn sodium. Each 8.1g canister delivers at least 112 metered sprays (56 doses); each 14.2g canister delivers at least 200 metered sprays (100 doses).

INDICATIONS AND USAGE: INTAL Inhaler is a prophylactic agent indicated in the management of patients with bronchial asthma.

CONTRAINDICATIONS: INTAL Inhaler is contraindicated in those patients who have shown hypersensitivity to cromolyn sodium or other components.

WARNINGS: INTAL Inhaler has no role in the treatment of an acute attack of asthma, especially status asthmaticus. Severe anaphylactic reactions can occur after cromolyn sodium administration. The recommended dosage should be decreased in patients with decreased renal or hepatic function. INTAL Inhaler should be discontinued if the patient develops eosinophilic pneumonia (or pulmonary infiltrates with eosinophilia). Because of the propellants in this preparation, it should be used with caution in patients with coronary artery disease or a history of cardiac arrhythmias.

PRECAUTIONS: General: In view of the biliary and renal routes of excretion for cromolyn sodium, consideration should be given to decreasing the dosage or discontinuing the administration of the drug in patients with impaired renal or hepatic function.

Occasionally, patients may experience cough and/or bronchospasm following cromolyn sodium inhalation. At times, patients who develop bronchospasm may not be able to continue administration despite prior bronchodilator administration. Rarely, very severe bronchospasm has been encountered.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long term studies in mice (12 months intraperitoneal treatment followed by 6 months observation), hamsters (12 months intraperitoneal treatment followed by 12 months observation), and rats (18 months subcutaneous treatment) showed no neoplastic effect of cromolyn sodium.

No evidence of chromosomal damage or cytotoxicity was obtained in various mutagenesis studies.

No evidence of impaired fertility was shown in laboratory animal reproduction studies.

Pregnancy: Pregnancy Category B. Reproduction studies with cromolyn sodium administered parenterally to pregnant mice, rats, and rabbits in doses up to 338 times the human clinical doses produced no evidence of fetal malformations. Adverse fetal effects (increased resorptions and decreased fetal weight) were noted only at the very high parenteral doses that produced maternal toxicity. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Drug Interaction During Pregnancy: Cromolyn sodium and isoproterenol were studied following subcutaneous injections in pregnant mice. Cromolyn sodium alone in doses of 60 to 540 mg/kg (38 to 338 times the human dose) did not cause significant increases in resorptions or major malformations. Isoproterenol alone at a dose of 2.7 mg/kg (90 times the human dose) increased both resorptions and malformations. The addition of cromolyn sodium (338 times the human dose) to isoproterenol (90 times the human dose) appears to have increased the incidence of both resorptions and malformations.

Nursing Mothers: It is not known whether this drug is excreted in human milk, therefore, caution should be exercised when INTAL Inhaler is administered to a nursing woman and the attending physician must make a benefit/risk assessment in regard to its use in this situation.

Pediatric Use: Safety and effectiveness in children below the age of 5 years have not been established. For young children unable to utilize the Inhaler, INTAL Nebulizer Solution (cromolyn sodium inhalation, USP) is recommended. Because of the possibility that adverse effects of this drug could become apparent only after many years, a benefit/risk consideration of the long-term use of INTAL Inhaler is particularly important in pediatric patients.

ADVERSE REACTIONS: In controlled clinical studies of INTAL Inhaler, the most frequently reported adverse reactions attributed to cromolyn sodium treatment were: throat irritation or dryness, bad taste, cough, wheeze, nausea.

The most frequently reported adverse reactions attributed to other forms of cromolyn sodium (on the basis of reoccurrence following readministration) involve the respiratory tract and are: bronchospasm [sometimes severe, associated with a precipitous fall in pulmonary function (FEV_1)], cough, laryngeal edema (rare), nasal congestion (sometimes severe), pharyngeal irritation and wheezing.

Adverse reactions which occur infrequently and are associated with administration of the drug are: anaphylaxis, angioedema, dizziness, dysuria and urinary frequency, joint swelling and pain, lacrimation, nausea and headache, rash, swollen parotid gland, urticaria, pulmonary infiltrates with eosinophilia, substernal burning, and myopathy.

The following adverse reactions have been reported as rare events and it is unclear whether they are attributable to the drug: anemia, exfoliative dermatitis, hemoptysis, hoarseness, myalgia, nephrosis, periarteritic vasculitis, pericarditis, peripheral neuritis, photodermatitis, sneezing, drowsiness, nasal itching, nasal bleeding, nasal burning, serum sickness, stomach ache, polymyositis, vertigo, and liver disease.

OVERDOSAGE: No action other than medical observation should be necessary.

DOSAGE AND ADMINISTRATION: For management of bronchial asthma in adults and children (5 years of age and over) who are able to use the Inhaler, the usual starting dosage is two metered sprays inhaled four times daily at regular intervals.

Patients with chronic asthma should be advised that the effect of INTAL Inhaler therapy is dependent upon its administration at regular intervals, as directed. INTAL Inhaler should be introduced into the patient's therapeutic regimen when the acute episode has been controlled, the airway has been cleared and the patient is able to inhale adequately.

For the prevention of acute bronchospasm which follows exercise, exposure to cold dry air or environmental agents, the usual dose is the inhalation of two metered dose sprays shortly, i.e., 10-15 minutes but not more than 60 minutes, before exposure to the precipitating factor.

INTAL INHALER THERAPY IN RELATION TO OTHER TREATMENTS FOR ASTHMA: Non-steroidal agents: INTAL Inhaler should be **added** to the patient's existing treatment regimen (e.g., bronchodilators). When a clinical response to INTAL Inhaler is evident, usually within two to four weeks, and if the asthma is under good control, an attempt may be made to decrease concomitant medication usage gradually.

Corticosteroids: In patients chronically receiving corticosteroids for the management of bronchial asthma, the dosage should be maintained following the introduction of INTAL Inhaler. If the patient improves, an attempt to decrease corticosteroids should be made.

It is particularly important that great care be exercised if for any reason cromolyn sodium is withdrawn in cases where its use has permitted a reduction in the maintenance dose of corticosteroids.

HOW SUPPLIED: INTAL Inhaler, 8.1g or 14.2g canister, box of one. Supplied with inhalation adapter and patient instructions.

NDC 0585-0675-01 14.2g canister NDC 0585-0675-02 8.1g canister

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Rev 7/86
FC 7518B

Reference: 1. Eigen H, Reid JJ, Dahl R, et al: Evaluation of the addition of cromolyn sodium to bronchodilator maintenance therapy in the long-term management of asthma. *J Allergy Clin Immunol* 1987;80:612–621.

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Editorials

Status Report on Phenylketonuria Treatment: 1990

In this issue of *AJDC*, the Writing Committee of the Collaborative Study of Children Treated for Phenylketonuria reports the status of 95 of these children who have reached age 12 years, a milepost age in the study.[1] At this point in the study, there were no surprises. However, the study has documented even more conclusively that (1) the sooner the low phenylalanine diet is begun, the better the outcome; (2) the longer a normal blood phenylalanine level is maintained, the better the outcome; and (3) termination of the diet has a deleterious effect. Because this collaborative study appears to be ending, I fear that it will be terminated prematurely.

See also p 35.

This carefully designed study was straightforward in concept and adequate for the knowledge and psychologic testing instruments of 1967. The planners underestimated the difficulty of maintaining near-normal blood phenylalanine levels in the 200 or more affected patients. This led to fewer patients in the continuously controlled group.

The current basic biochemical research and new understanding of the biochemical defects of phenylketonuria could not have been fully anticipated in 1967. We now know that the apoenzyme (phenylalanine hydroxylase) and generation of the cofactor (tetrahydrobiopterin) had several defects, most causing different clinical expressions. Most expressions of these defects would have allowed children with different molecular defects to be included in the study. Thus, it has been a study of several hyperphenylalanemias and not of a single disorder.

Use of a low-phenylalanine diet is still the only practical, available mode of treatment, and the experiences of most clinics today are similar to those documented in this study. However, the study in its original design does not address the late findings that are surfacing in the phenylketonuric patients. The fact is that these patients usually are not truly normal. This is hinted at in the committee's report that the children show deficiencies in mathematic performance. Others have revealed that older, well-treated patients have performance deficits in conceptual, visuospatial, and language skills. In light of these findings, the study now could be redesigned to include the newer and more revealing neuropsychologic testing instruments as well as the traditional instruments employed in the study. This is an important cohort of patients that should be followed up for at least another decade.

C. Charlton Mabry, MD
University of Kentucky
Department of Pediatrics
Endocrinology & Metabolism
800 Rose St
Lexington, KY 40536-0084

Reference

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Development, Growth, and Cardiac Surgery

In this issue of *AJDC*, Mendoza and coworkers report the results of neurodevelopmental testing and somatic growth in 24 of 27 late survivors of arterial switch operations for transposition of the great arteries performed at Korsair Children's Hospital, Louisville, Ky. Six early deaths (18.2%) occurred among the 33 patients who underwent arterial switch operations, and three patients did not undergo follow-up testing. The data show that 18 (75%) had normal growth, while six had small head circumference. Developmental scores were within one SD of normal for 18 patients. Of the remaining six, three had scores between one and two SDs below normal, and three had scores that were greater than two SDs below normal. Previous reports[1,2] provide some information about developmental outcomes of patients who underwent cardiac repairs in infancy, but very little information about patients who underwent neonatal repair. In the report by Mendoza et al, all but three of the patients for whom follow-up data were available were neonates.

See also p 40.

The factors affecting neurodevelopment (and perhaps, indirectly, body size and head circumference) after neonatal cardiac surgery are undoubtedly complex, but likely involve the interactions of preoperative, intraoperative, and postoperative factors. There is no reason to believe that in utero neurologic development is impaired in patients with transposed great arteries, and one study[1] suggests that most patients undergoing early atrial level repair have normal results of neurologic development tests. I believe the authors are correct to point out the importance of preoperative events in determining neurologic outcome. Review of their data shows that four of the six patients with less favorable outcomes had either preoperative seizures (two patients) or sufficiently severe acidosis and/or hypoxia to require an emergency balloon atrial septostomy (one patient) or an emergency arterial switch operation (one patient).

Intraoperative events related to cardiopulmonary bypass, such as air or particulate embolism, time of circulatory arrest, and use of hypothermia alone, have been thought to affect postoperative outcome.[3] Unfortunately, the report by Mendoza et al contains only data on the depth of hypothermia (16°C to 18°C) and the average time of cardiopulmonary bypass. Neither were related to outcome in this study. Many surgical groups, including our own, use deep hypothermia with periods of circulatory arrest of up to 60 minutes for neonatal repairs of various defects.[3-6] However, hypothermia alone was initially thought to have a markedly adverse impact on neurologic outcome in reports by Bjork and Hultquist[7] and Egerton et al.[8] Other theoretically important factors during bypass may include acid-base (carbon dioxide) management during hypothermia,[9-11] perfusion pressure (particularly after a period of ischemia),[12,13] and pharmacologic interventions such as α-adrenergic blockade,[14] pretreatment with corticosteroids,[15] and use of mannitol (as a free radical scavenger).[16] All three of these pharmacologic interventions as well as the "alpha-stat" strategy of pH and P_{CO_2} management during hypothermia are used in our institution, although clear-cut data supporting their use is lacking. Undoubtedly, many other intraoperative variables may effect outcome, either alone or in combination.

Finally, the effect of postoperative events on outcome is demonstrated in patient 8 in the report by Mendoza et al. It is equally noteworthy, however, that seizures alone did not predict outcome. Only one of the three patients in this study who had postoperative seizures showed a subsequent developmental abnormality. This experience is similar to that generally quoted in current texts.[3]

These comments are offered primarily to emphasize that multiple preoperative, intraoperative, and postoperative variables may influence neurologic outcome in a complex manner. Multivariate analyses should generally be employed to assess the impact of any single variable or combination of variables. The report by Mendoza et al contains neither sufficient numbers of patients nor sufficient data on potentially important variables such as those outlined above to conduct a multivariate analysis. Therefore, the effect of any of the variables described in this report on the ultimate neurologic outcome cannot be assessed with certainty. It is to be emphasized that as many details as possible concerning the management of bypass and circulatory arrest, including both physical and pharmacologic interventions, should be included in reports such as these. The early poor experience with deep hypothermia[7,8] was probably due, in retrospect, to the failure to employ as simple a measure as hemodilution during hypothermic perfusion. Because our understanding of the complex events occurring during cardiopulmonary bypass and deep hypothermia (with or without circulatory arrest) is incomplete, reporting the details of perfusion management may allow both insights into pathophysiologic mechanisms and meaningful comparisons of the experiences at different centers. Despite many such details being excluded from this report, the descriptive data on outcome will be a useful basis for comparison in subsequent studies. Much more extensive data on neurologic outcome after neonatal cardiac surgery is necessary before any firm conclusion as to its safety can be reached, but these follow-up data are encouraging and confirm my own clinical impression that neonatal cardiac operations using cardiopulmonary bypass and deep hypothermia are associated with good neurologic outcome in most instances. As the potential benefits of early primary correction of congenital heart defects are now becoming clearer,[4] better understanding of the techniques of hypothermic cardiopulmonary bypass and circulatory arrest that are necessary to effect such repairs in neonates now assume even greater importance. More reports, such as that by Mendoza et al, will (I hope) further our knowledge in this important area.

JOHN E. MAYER, JR, MD
The Children's Hospital
Department of Cardiovascular Surgery
300 Longwood Ave
Boston, MA 02115

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Intellectual Development in 12-Year-Old Children Treated for Phenylketonuria

Colleen G. Azen, MS; Richard Koch, MD; Eva Gross Friedman; Stanley Berlow, MD; James Coldwell, MD; Wilma Krause, MD; Reuben Matalon, MD, PhD; Edward McCabe, MD, PhD; Margaret O'Flynn, MD; Raymond Peterson, MD; Bobbye Rouse, MD; C. Ronald Scott, MD; Bernice Sigman, MD; David Valle, MD; Robert Warner, MD

• Intelligence and achievement test scores were evaluated for 95 12-year-old children with phenylketonuria who had begun dietary therapy during the neonatal period. Dietary control of blood phenylalanine below 900 μmol/L was maintained beyond age 10 years in 23 children; 72 others had blood phenylalanine persistently above that level at ages ranging from 18 months to 10 years. Test scores at age 12 years were negatively correlated with the age at initiation of diet and with blood phenylalanine levels from ages 4 to 10 years, and positively correlated with parent IQ scores and the age at loss of dietary control. Children who maintained phenylalanine levels below 900 μmol/L beyond age 10 years showed no deficits in test scores, except for arithmetic, the scores of which declined between ages 6 and 12 years in 90% of the children in this study. These data strongly support a recommendation that dietary restriction of phenylalanine should be maintained through adolescence.

(*AJDC*. 1991;145:35-39)

Early diagnosis and treatment of children with phenylketonuria (PKU) has been regarded as a model of successful intervention in the prevention of mental retardation. Treatment consists of initiating a restricted phenylalanine (PHE) diet as early as possible after birth and maintaining blood PHE levels between 120 and 600 μmol/L. Discontinuation or relaxation of the PHE-restricted diet at ages varying from 4 to 10 years had been common practice in the United States for many years. However, a change in this approach has been occurring since 1977/1978, when Cabalska et al[1] and Smith et al[2] reported deteriorating IQ scores in children with PKU after diet termination. In 1980, Waisbren et al[3] reviewed 19 published studies of diet discontinuation, nine of which reported significant declines in intelligence test scores of children with PKU when diet therapy was discontinued.

A report from the Collaborative Study of Children Treated for Phenylketonuria (PKUCS) by Holtzman et al[4] in 1986 showed strong correlations between the age at loss of dietary control and cognitive test scores at ages 8 and 10 years. Fishler et al[5] found that, in this same group of children with PKU, those who stayed on diet had higher reading and spelling scores at age 10 years in comparison with diet discontinuers, but that arithmetic, language, and perceptual test scores declined uniformly for both groups from ages 6 to 10 years. Subsequent data from Germany,[6] Ireland,[7] and the United States[8] support the efficacy of maintaining dietary restriction of PHE throughout childhood and adolescence. However, in France, where diet discontinuation remains common, a recent study[9] found no evidence of deteriorating IQ when therapy was discontinued at 5 to 8 years, although perceptual motor dysfunction and learning disabilities were noted. Koch et al[10] reported higher scores on most intelligence and academic achievement tests in 12-year-old PKUCS patients who maintained dietary restriction of PHE through age 8, in contrast to those who had lost dietary control at earlier ages. In this report, we further investigate the relationship between test scores in 12-year-old PKUCS children and a number of other factors describing the diagnosis and treatment history of children with PKU, as well as their social and intellectual environment.

PATIENTS AND METHODS

Study Design and Patients

The Collaborative Study of Children Treated for PKU was initiated in 1967 at 16 treatment centers throughout the United States to investigate prospectively the effects of dietary restriction of PHE on the growth and development of children with PKU. Details of the study design and results have been published.[4,5,11-14] All patients were identified by newborn screening and began dietary therapy before age 120 days. Sample acquisition was completed in 1972 with the enrollment of 167 children with classic PKU. Ninety-five PKUCS patients whose psychologic test scores were available at age 12 years were evaluated for this report.

The study was conducted in two phases. During phase A, each child was randomly assigned to maintain average blood PHE levels either between 60 and 332 μmol/L or between 330 and 599 μmol/L until age 6 years. In phase B, children were randomly assigned at age 6 years either to continue the diet therapy to maintain blood PHE levels ideally below 720 μmol/L, or to discontinue diet therapy, with annual follow-up evaluations. Due to parental consent requirements, this randomization was disrupted by some parents choosing to either continue or discontinue diet therapy regardless of assignment. However, no child was dropped from the study because of failure to comply with randomization.

Throughout phases A and B, dietary compliance was assessed by monitoring blood PHE levels as follows: weekly during the first year of life and monthly thereafter, with quarterly assessments obtained after diet termination. For each child, the median PHE

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From the Division of Medical Genetics, Children's Hospital of Los Angeles, Calif (Mss Azen and Friedman and Dr Koch); the universities of Wisconsin, Madison, (Dr Berlow), Colorado, Denver (Dr McCabe), Texas, Galveston (Dr Rouse), Iowa, Iowa City (Dr Krause), Washington, Seattle (Dr Scott), Maryland, Baltimore (Dr Sigman), and Illinois, Chicago (Dr Matalon); Children's Medical Center, Tulsa, Okla (Dr Coldwell); Children's Hospital, Los Angeles (Dr O'Flynn); Children's Hospital Health Center, San Diego, Calif (Dr Peterson); the Johns Hopkins Hospital, Baltimore, Md (Dr Valle); and Children's Hospital, Buffalo, NY (Dr Warner).

A complete list of institutions participating in this research study appears on page 39.

Reprint requests to Maternal PKU Collaborative Study, Division of Medical Genetics, Children's Hospital of Los Angeles, 4650 Sunset Blvd, Los Angeles, CA 90027 (Ms Azen).

level during each 6-month period constituted an index of dietary control (IDC) for that period.

Variables Used in Analyses

Outcome variables selected for evaluation in this report were Wechsler Intelligence Scale for Children–Revised (WISC-R)[15] IQ scores and Wide Range Achievement Test (WRAT)[16] standard scores at age 12 years. We also evaluated the change in test scores between ages 6 and 12 years, and the difference between the 12-year IQ scores of children with PKU and those of their parents. Scores for children with PKU at 6 years were measured by the 1972 norms of the Stanford-Binet Intelligence Scale,[17] and parental IQ was assessed with the Wechsler Adult Intelligence Scale (WAIS).[18] When IQ scores were available for both parents, their average scores were used as parent IQ; otherwise, the single available parent's scores were used.

Independent variables describing the diagnosis and treatment of the child with PKU included maximum diagnostic PHE level; maximum and 48-hour blood PHE levels during PHE challenges at ages 3 months and 1 year; age at initiation of diet; IDCs for 6-month periods ending at ages 2, 4, 6, 8, and 10 years; average IDC before age 4 years; average IDC between ages 4 and 6 years; average IDC between ages 6 and 10 years; and the age at which dietary control was lost. Loss of dietary control was defined in an earlier PKUCS report[4] as the age at the beginning of the first of three consecutive 6-month periods during which the IDC exceeded 900 µmol/L, regardless of whether the child was still receiving a PHE-restricted diet. Blood PHE levels after age 10 years were unavailable for one third of the sample, and were excluded from those multivariate analyses requiring complete data for all cases, to maintain maximum sample sizes. Most children with no reported PHE levels after age 10 years had discontinued treatment before that age. Levels after 10 years were comparable with 10-year levels in those for whom these data were available. Variables describing the environment of the child with PKU were parents' WAIS IQ scores, Hollingshead two-factor index of socioeconomic status (Hollingshead AB, unpublished data, 1957), and the family coping pattern, which was assessed by consensus of the clinic team on a four-point scale from adequate to dysfunctional.

Although the study was designed as a randomized trial, considerable deviation from dietary group assignments occurred toward the end of phase A and throughout phase B. Those who maintained their random assignment (65%) were comparable with those who declined or switched groups (35%) on the basis of sex, birth order, parental age, and IQ. There was a tendency for families who did not accept randomization to have higher socioeconomic status and better family coping pattern scores.

Table 1.—Multiple Regression Analyses for Cognitive and Achievement Test Scores in Children With Phenylketonuria*

	WISC-R IQ Scores (n=91)			WRAT Standard Scores (n=84)		
	Verbal	**Performance**	**Full Scale**	**Reading**	**Spelling**	**Arithmetic**
Partial correlation coefficient for:						
Parent IQ	0.36 (<.01)	0.47 (<.01)	0.47 (<.01)	0.39 (<.01)	0.33 (<.01)	0.33 (<.01)
Age when first treated	−0.17 (.04)	−0.23 (.01)	−0.22 (.01)	−0.17 (.07)	−0.28 (<.01)	−0.18 (.08)
Age at loss of dietary control	0.18 (.14)	0.22 (.01)	0.31 (<.01)	0.38 (<.01)	0.26 (.01)	0.10 (.36)
IDC between 4 and 6 y	−0.27 (.03)	. . .	. . .	. . .	. . .	. . .
R^2	.43	.38	.45	.36	.29	.17

*Numbers in parentheses are *P* values. WISC-R indicates Weschler Intelligence Scale for Children–Revised; WRAT, Wide Range Achievement Test; and IDC, index of dietary control.

Statistical Analysis

Test scores at age 12 years were evaluated as data from an observational study, ie, one group of children with PKU with varying degrees of dietary control throughout childhood along with other factors that may affect cognitive development. Probability values reported for statistical tests should be interpreted accordingly. Results were considered statistically significant at $P<.05$. While it is recognized that performing many statistical tests increases the risk of erroneously detecting significant results, the majority of significant results in this report had probability values too small to be explained by this factor alone.

For each outcome variable, stepwise regression was used to identify a subset of diagnostic, treatment, and social factors that contributed significantly to 12-year test scores. Multiple regression was then employed to evaluate the relative importance of each significant predictor variable to each of the outcome variables. A logarithmic transformation was applied to the age at initiation of treatment since the transformed data better fit a normal distribution.

Comparisons among three subgroups, defined on the basis of age at loss of dietary control, were made by one-way analysis of variance, with Bonferroni adjustment of probability values for pairwise group comparisons. Within each group, paired *t* tests were used to compare test scores at ages 6 and 12 years, and to compare the IQ scores of the child with PKU with those of his or her parents. Nonparametric tests were also employed where appropriate. Statistical analyses were performed using the Statistical Analysis System (SAS Institute, Cary, NC)[19] and BMDP computer programs (BMDP Statistical Software, Los Angeles, Calif).[20]

RESULTS

Families of children who participated in this study were primarily middle-class, with a shift toward the lower end of the Hollingshead Scale (62% fell in the two lowest categories; 14% in the two upper categories). Parents' WAIS IQ scores were above average (mean ± SD, 108 ± 11). The majority (56%) of these families were judged to have adequate coping skills by their respective clinic teams, 28% were considered to have minor coping problems, 14% had major problems in fulfilling marital or parental roles, and one family was judged dysfunctional.

All patients who remained active in the study through age 12 years had started receiving therapy prior to age 65 days (median, 17 days; range, 3 to 64 days). Maximum diagnostic PHE levels ranged from 1380 to 5340 µmol/L (mean ± SD, 2760 ± 720 µmol/L). Mean IDC values for the group rose from 402 ± 174 µmol/L at age 1 year to 714 ± 270 µmol/L at age 6 years. During phase B, the average IDC for children continuing therapy was 750 ± 318 µmol/L. Children who discontinued therapy exhibited a sharp rise in PHE, to a mean IDC level of 1584 ± 354 µmol/L.

Stepwise regression for each outcome variable showed that parent IQ was the strongest predictor of test scores at age 12 years. After entering parent IQ into

Table 2.—Treatment History of 12-Year-Old Children With Phenylketonuria Grouped by Age at Loss of Dietary Control*

	Group 1 (n=23)	Group 2 (n=47)	Group 3 (n=25)
Age first treated, d			
Median	23	17	14
Range	3-55	5-64	4-54
Maximum diagnostic phenylalanine levels, μmol/L			
Mean	2820	2820	2520
SD	780	720	660
Average blood phenylalanine levels between specified ages, μmol/L			
Diagnosis to 4 y			
Mean	576	462	354
SD	150	90	108
4 to 6 y			
Mean	912	564	462
SD	192	120	150
6 to 10 y			
Mean	1554	1326	600
SD	282	324	144
After 10 y	n=8	n=32	n=20
Mean	1554	1368	750
SD	372	342	270

*Group 1 includes patients who lost dietary control prior to age 6 years; group 2, between ages 6 and 10 years; and group 3, after age 10 years.

Table 3.—Mean 12-Year WISC-R, WRAT, and Parent WAIS IQ Scores for PKUCS Children Grouped by Age at Loss of Dietary Control*

	Group 1	Group 2	Group 3	ANOVA *P*
WISC-R IQ Scores	n=23	n=47	n=25	. . .
Verbal	85±15	95±14	101±11	.0004
Performance	92±15	95±14	101±11	.0499
Full scale	87±14	96±14	101±11	.0028
WRAT standard scores	n=22	n=46	n=20	. . .
Reading	92±13	97±11	105±12	.0029
Spelling	87±17	92±13	98±17	.0452
Arithmetic	80±11	82±11	84±10	.6033
Parent WAIS IQ scores	n=23	n=43	n=25	. . .
Full scale	104±10	109±9	108±14	.1905

*Group 1 includes patients who lost dietary control prior to age 6 years; group 2, between ages 6 and 10 years; and group 3, after age 10 years. WISC-R indicates Weschler Intelligence Scale for Children–Revised; WRAT, Wide Range Achievement Test; and WAIS, Weschler Adult Intelligence Scale; and PKUCS, Collaborative Study of Children Treated for Phenylketonuria. Values are means±SDs.

the regression equation, age at initiation of treatment was the next most significant predictor of dependent variables—spelling, arithmetic, and performance IQ scores—followed by age at loss of dietary control. When the dependent variable was reading, verbal IQ, or full scale IQ score, the order of entry into the regression equation was as follows: parent IQ, age at loss of dietary control, and age at initiation of treatment. Average IDC between 4 and 6 years had additional predictive power for verbal IQ. No other variables significantly improved any of the regression equations.

Table 1 summarizes multiple regression analyses for each outcome variable regressed on parent IQ and other variables identified by the stepwise procedure as contributing significantly to outcome. The partial correlation coefficients indicate the strength of the relationship between outcome and each independent variable after the remaining independent variables have been entered into the regression equation. For example, the correlation between age when first treated and full scale IQ after controlling for parent IQ and age at loss of dietary control was −.22 ($P=.01$). Among this set of variables, parent IQ had the highest partial correlation with each of the outcome variables, although age at loss of dietary control was nearly as highly correlated with reading. The percent of total variation in the outcome variables explained by the predictor variables (R^2) ranged from 17% for arithmetic to 45% for WISC-R full-scale IQ.

Further analyses were performed for the following three groups of PKUCS children: those who lost dietary control prior to age 6 years (group 1), between ages 6 and 10 years (group 2), and after age 10 years or not at all (group 3). The groups did not differ in age first treated or maximum diagnostic PHE (Table 2), but IDCs were consistently higher in group 1 than in groups 2 and 3 before age 4 years, between ages 4 and 6 years, and after age 6 years. Group 2 IDCs were also higher than those in group 3 at all ages.

Twelve-year WISC-R and WRAT mean test scores for groups 1, 2, and 3 are shown in Table 3. In all cases, group 1 had the lowest mean scores; group 3, which maintained dietary control at least through age 10 years, had the highest scores; and group 2 had mean scores falling between those of groups 1 and 2. Statistically significant differences by one-way analysis of variance were noted across groups for all of the 12-year test scores with the exception of arithmetic. The differences were primarily between groups 1 and 3, with significant differences also noted between groups 1 and 2 on WISC-R verbal and full-scale IQ scores, and between groups 2 and 3 on reading. Groups 2 and 3 did not differ significantly on any of the other 12-year test scores.

Scores on the WISC-R for children with PKU at age 12 years were compared with WAIS scores of their parents as an indication of the cognitive development of the child with PKU relative to other family members. Statistically significant deficits were observed on all three scales for all of the groups. The greatest differences were for group 1, followed by groups 2 and 3 (Table 4). Some of the apparent discrepancy may be attributed to the use at age 12 years of the revised WISC, which, on average, has been shown to produce scores approximately eight points lower than those attained by the same children on the unrevised WISC.[21]

Table 4.—Differences Between WISC-R Scores in 12-Year-Old Children With PKU and Their Parents on Comparable WAIS IQ Scales*

IQ Scale	Group 1 (n=23)	Group 2 (n=43)	Group 3 (n=25)
Verbal	−19±14 (.0001)	−13±12 (.0001)	−7±15 (.0191)
Performance	−12±16 (.0014)	−11±12 (.0001)	−7±11 (.0047)
Full	−17±14 (.0001)	−13±11 (.0001)	−8±12 (.0027)

*Group 1 includes patients who lost dietary control prior to age 6 years; group 2, between ages 6 and 10 years; and group 3, after 10 years. WISC-R indicates Weschler Intelligence Scale for Children–Revised; PKU, phenylketonuria; and WAIS, Weschler Adult Intelligence Scale. Values are mean (±SD) child minus parent differences. Numbers in parentheses are *P* values.

Table 5.—Changes in Test Scores Between Ages 6 and 12 Years for PKUCS Children Grouped by Age at Loss of Dietary Control*

IQ Test	Group 1	Group 2	Group 3
WISC-R vs Stanford-Binet	n=22 −4±6 (.0187)	n=47 −4±11 (.0085)	n=25 −1±10 (.6653)
WRAT	n=22	n=46	n=19
Reading	−6±14 (.0446)	−10±13 (.0001)	0±14 (.9501)
Spelling	−5±21 (.3136)	−8±14 (.0006)	1±16 (.7262)
Arithmetic	−11±15 (.0023)	−18±11 (.0001)	−16±12 (.0001)

*Group 1 includes patients who lost dietary control prior to age 6 years; group 2, between ages 6 and 10 years; and group 3, after age 10 years. PKUCS indicates collaborative study of Children Treated for Phenylketonuria; WISC-R, Weschler Intelligence Scale for Children–Revised; and WRAT, Wide Range Achievement Test. Values are mean (±SD) 12-years minus 6-years differences. Numbers in parentheses are *P* values.

At age 6 years, groups 2 and 3 had comparable mean scores on all tests (IQ, 100±14 vs 101±14; reading, 106±17 vs 105±13; spelling, 100±15 vs 99±13; and arithmetic, 100±13 vs 100±9), but mean scores for group 1, which had already lost dietary control, were six to 10 points lower (IQ, 91±15; reading, 99±20; spelling, 91±23; and arithmetic, 92±17). The differences in mean 6-year scores between group 1 and groups 2 and 3 combined were statistically significant for IQ ($P=.01$), spelling ($P=.01$), and arithmetic ($P=.03$), and approached significance for reading ($P=.05$).

Between ages 6 and 12 years, both groups of children who had lost dietary control had statistically significant drops in all areas, with the exception of spelling for group 1 (Table 5). The greatest overall declines were seen in group 2, the patients who lost control between ages 6 and 10 years. All groups showed significant declines in arithmetic scores.

COMMENT

For children with PKU, these data clearly show an association between exposure to high PHE levels prior to age 12 years and loss of cognitive and academic performance as measured by the WISC-R and WRAT tests. In this group of children, test scores at 12 years of age were negatively correlated with the age at which PHE restriction was begun. After treatment was begun, longer exposure to levels above 900 µmol/L was also associated with lower test scores at age 12 years.

It should be noted that the selection of PHE levels consistently above 900 µmol/L as an operational definition of loss of dietary control does not imply that any level up to that cutoff is safe, particularly at earlier ages. Indeed, Holtzman et al,[4] in their study of PKUCS children at ages 8 and 10 years, found similar results using 780 µmol/L as a cutoff for dietary control. They further pointed out that the small number of PKUCS children whose PHE levels exceeded 600 µmol/L after initiation of diet in the first years of life made it difficult to adequately assess lower thresholds at early ages. A similar problem was encountered in the present analyses in attempting to distinguish between 8 and 10 years as a critical age for maintaining dietary control. Only five children were in good control at age 8 years, but not at age 10 years—too few to form a separate group for analysis. Their pattern of test scores was similar to that of children who lost dietary control between ages 6 and 8 years and, hence, they were included with that group.

The greatest deficits at age 12 years were seen in those children whose levels exceeded 900 µmol/L before age 6 years. Test scores of these children were reduced at age 6 years and continued to decline until age 12 years. Children who maintained dietary control until age 6 years, but lost dietary control between ages 6 and 10 years, showed no differences in 6-year test scores compared with those who never lost dietary control. However, at age 12 years, they had significantly lower test scores and greater deviations from parent IQ. The greatest decreases in test scores between ages 6 and 12 years were seen in this group of children.

Some of the difference between IQ scores at ages 6 and 12 years may reflect different test content between the Stanford-Binet and the WISC-R, as well as a real decline in general cognitive ability. Nevertheless, children who maintained PHE levels below 900 µmol/L at least through age 10 years had the highest scores at age 12 years, showed little or no change in test scores between ages 6 and 12 years (except for arithmetic), and had 12-year mean IQ scores nearly comparable with those of their parents. In fact, an upward adjustment of WISC-R scores by the six-point difference reported between WISC-R and WAIS scores in nonretarded individuals[21] would have eliminated most of the child-parent IQ deficit in this group of children, but not in the other two groups.

Arithmetic was the only area of cognitive functioning evaluated at age 12 years for which maintaining dietary control of PHE below 900 µmol/L had no apparent beneficial effect. Mean scores declined significantly in all groups. In fact, all but eight of these children had lower arithmetic scores at age 12 years than at age 6 years. More than two thirds experienced a drop in arithmetic scores of 10 or more points. This finding is consistent with an earlier report of scores on arithmetic, perception, and linguistic tests declining between ages 6 and 10 years at similar rates for PKUCS children on and off diets.[5] The decline in arithmetic scores may be due to some aspect of test content at age 12 years that is particularly sensitive to even moderate elevations in PHE levels. A pilot study by Pennington et al[22] found children with PKU treated early to be deficient in certain cognitive and visuospatial skills that would be included in achievement tests at age 12 years but not at age 6 years.

The pattern of cognitive test scores observed in PKUCS children at age 12 years indicates that optimal intellectual and academic achievement are obtained by the earliest possible initiation of treatment and strict control of blood PHE levels throughout childhood. This conclusion is supported by the recent studies by Krause and coworkers[23] and Lou et al.[24] They independently demonstrated significant psychoneurologic changes associated with elevated blood levels of PHE. Another reason for continuation or resumption of dietary therapy, based on clinical experience with older off-diet individuals with PKU, is the devastating effects on offspring of untreated pregnant women with PKU.[25]

It is estimated that some 2700 women with PKU will be of childbearing age in the next two decades. In fact, Kirkman[26] has projected that unless a therapeutic remedy is developed soon, the beneficial results of the newborn screening programs for PKU will be neutralized by the birth of mentally retarded children to women with PKU. The problem of maternal PKU is now the subject of a national study sponsored by the National Institute of Child Health and Human Development.[27] The project encompasses all US states and Canadian provinces, and will ascertain whether therapy with the PHE-restricted diet protects fetal development and improves outcome so that physicians can properly advise the women with PKU approaching reproductive age.

The clinician now has data to recommend continuation of a diet restricted in PHE through age 12 years. While extended therapy is exceedingly important, particularly for women during their reproductive years, it certainly is not easily accomplished. In fact, many teenagers with PKU literally remove themselves from dietary therapy despite medical advice to the contrary. Attempts to reinstitute the PHE-restricted diet for prolonged periods have met with limited success.[28] Individuals with PKU, as well as their families, should receive counseling and support from the clinic team to facilitate the maintenance of extended therapy.

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Participating Centers

Project Staff.—Richard Koch, MD, Medical Director; Malcolm Williamson, PhD, Codirector; Eva Gross Friedman, Associate Director; Colleen Azen, MS, Coordinator, biostatistics.

Laboratory Directors.—Samuel Bessman, MD, Director, Serum/Blood Reference Laboratory, University of Southern California, Los Angeles; Kenneth Shaw, PhD, Director, Urine Chromatography Reference Laboratory, Childrens Hospital of Los Angeles.

Consultants.—*Nutrition:* Phyllis Acosta, DrPH, Florida State University, Tallahassee; *Education:* Robert Henderson, EdD, University of Illinois, Champaign; *Genetics:* Neil A. Holtzman, MD, MPH, Johns Hopkins University School of Medicine, Baltimore, Md; *Biostatistics:* Richard Kronmal, PhD, University of Washington, Seattle; *Psychology:* William van Doorninck, PhD, University of Colorado, Denver.

Clinic Directors.—Stanley Berlow, MD, University of Wisconsin, Madison; James Coldwell, MD, Childrens Medical Center, Tulsa, Oklahoma; Edward McCabe, MD, PhD, University of Colorado, Denver; Bobbye Rouse, MD, University of Texas, Galveston; Wilma Krause, MD, University of Iowa, Iowa City; Carol Shear, MD, University of Miami (Fla); C. Ronald Scott, MD, University of Washington, Seattle; Richard Koch, MD, Childrens Hospital, Los Angeles; Margaret O'Flynn, MD, Childrens Memorial Hospital, Chicago, Ill; Raymond Peterson, MD, Childrens Hospital Health Center, San Diego, Calif; Bernice Sigman, MD, University of Maryland School of Medicine, Baltimore; David Valle, MD, The Johns Hopkins Hospital, Baltimore; Robert Warner, MD, Childrens Hospital, Buffalo, NY; Reuben Matalon, MD, PhD, University of Illinois Hospital, Chicago.

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Follow-up of Patients Who Underwent Arterial Switch Repair for Transposition of the Great Arteries

Julita C. Mendoza, MD; Shirley A. Wilkerson, MD, PhD; Anabel H. Reese, MEd

• Thirty infants underwent arterial switch for transposition of the great arteries within the first week of life (mean age, 2.8 days). An additional three patients underwent repair at 5½, 8, and 9½ months of age. Six (18.2%) of 33 patients died. All the survivors were not receiving cardiac medications or diuretics at the time of the last follow-up visit. Examination of 24 of 27 survivors at 1 to 5 years of age revealed normal growth in 75% of the patients. Two patients had height, weight, and head circumference below the fifth percentile for age. Four patients had height and weight appropriate for age but head circumference below the fifth percentile. Neurodevelopmental testing yielded normal findings in 18 patients. Three patients were considered suspect and an additional three were abnormal neurodevelopmentally. Head circumference less than the fifth percentile, abnormalities on computed tomographic scans of the brain, and emergency balloon atrial septostomy or emergency switch operation were more likely to occur in patients who had low neurodevelopmental scores. We conclude that the majority of patients who undergo arterial switch repair demonstrate normal growth and development and no impairment of cardiovascular function. However, significant morbidity in the form of neurodevelopmental problems may occur.

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Transposition of the great arteries (TGA) is one of the most common cyanotic congenital heart defects, occurring in 1 in 2300 to 1 in 5000 live births.[1] Without intervention, the mortality rate is 90% before 6 months of age.[2,3] The use of prostaglandin E_1 to maintain patency of the ductus[4-6] and the performance of balloon atrial septostomy (BAS)[7] at the time of cardiac catheterization permit mixing of the pulmonary and systemic circulations, resulting in increased arterial oxygen saturation, thereby improving the general status and increasing the chances of survival before corrective surgery in these critically sick neonates.

Infants with TGA usually present shortly after birth with cyanosis and respiratory distress. A number of them have severe hypoxia and metabolic acidosis and will die unless their arterial oxygen saturation is improved. In our institution, infants undergo an arterial switch operation for simple TGA. We performed this study to determine the outcome in the first 33 infants who underwent this corrective procedure and to describe its effects on the growth and neurodevelopment of the survivors.

PATIENTS AND METHODS

Patients

Thirty-three patients with TGA underwent an arterial switch operation between November 1983 and October 1988 (Table 1). The gestational ages of the infants ranged from 36 to 41 weeks (mean, 39.8 weeks) and the birth weight ranged from 2.3 to 4.2 kg (mean, 3.48 kg). All the infants had weight, length, and head circumference within or above the normal range for gestational age at birth. Twenty-seven patients had simple TGA (with an intact ventricular septum) and six had TGA associated with a ventricular septal defect.

Preoperative Evaluation and Management

All patients underwent echocardiography on admission to the intensive care nursery, and all underwent cardiac catheterization before operation. Balloon atrial septostomy was performed in 24 patients (72.7%) at the time of catheterization, five of which were performed emergently due to severe hypoxia and metabolic acidosis. Prostaglandin E_1 was administered preoperatively in 30 patients.

The patients with simple TGA underwent repair within the first week of life, at a mean age of 2.8 days. Among the six patients with TGA and a ventricular septal defect, three had a moderate to large septal defect and were operated on at 5½, 8, and 9½ months of age. Five patients underwent emergency arterial switch operation due to severe hypoxia and acidosis despite prostaglandin E_1 infusion and BAS.

The operation was performed with the use of cardiopulmonary bypass and deep systemic hypothermia with core cooling to 16°C to 18°C. Duration of bypass surgery ranged from 50 minutes to 6 hours (mean, 2.4 hours). Aortic cross-clamp time was generally less than 60 minutes. The procedure consisted of the arterial switch repair introduced by Jatene et al[8] in 1975 and modified by Castaneda et al[9] and Mavroudis,[10] with excision of the two coronary arteries from the aorta and their implantation to the pulmonary artery, transection of the aorta and the pulmonary artery, and, finally, anastomoses between the pulmonary artery stump and the distal aorta and between the stump of the aorta and the distal end of the pulmonary artery. The Lecompte maneuver[11] was also employed, passing the ascending aorta posterior to the pulmonary artery birfurcation. Pericardial tissue was used as necessary in the arterial reconstruction.

All patients underwent ventilation for 2 to 27 days (mean, 7.4 days) after the operation and all required inotropic support. Nine patients were treated with digoxin and/or a diuretic agent until 4 to 18 months of age.

Follow-up

In addition to their cardiology follow-up, the survivors were seen in our neonatal follow-up clinic. Growth variables (weight, height, and head circumference) were plotted. Physical and neurologic examinations were performed by a neonatologist or neonatal fellow. Neurodevelopmental progress was evaluated by an experienced developmental psychologist with use of the Bayley Scales of Infant Development[12] for patients up to 2 years of age and the Stanford-Binet Intelligence Scale[13] and Denver Developmental Screening Test[14] for those older than 2 years. Functional cardiac status was also determined from cardiology records.

RESULTS

Mortality

Six (18.2%) of the 33 patients died (Table 2). Two deaths occurred among the first 15 patients who underwent the arterial switch procedure; the other

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From the Division of Neonatology, Department of Pediatrics, University of Louisville (Ky).

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Reprint requests to the Department of Pediatrics, School of Medicine, University of Louisville, Louisville, KY 40292 (Dr Wilkerson).

Table 1.—Characteristics of Infants Who Underwent Arterial Switch Repair for Transposition of the Great Arteries (TGA)*

Variable	Value
Total No. of patients	33
Birth weight, g	3476.0±512
Gestational age, wk	39.8±0.9
Sex	
M	24 (72.7)
F	9 (27.3)
Preoperative evaluation	
Echocardiography	33 (100)
Cardiac catheterization	33 (100)
With BAS	24 (72.7)
Without BAS	9 (27.3)
PGE$_1$ infusion	30 (90.9)
Diagnosis	
TGA with IVS	27
TGA with VSD	6
Age at surgery, d	
TGA with IVS or small VSD	2.8±1.7
TGA with moderate/large VSD	230.6±61.1

*Values represent number (percent) or mean±SD. BAS indicates balloon atrial septostomy; PGE$_1$, prostaglandin E$_1$; IVS, intact ventricular septum; and VSD, ventricular septal defect.

Table 2.—Details of Six Deaths After Arterial Switch Repair*

Patient	Timing of Death	Age at Death, d	Cause of Death
1	Early postoperative period	4	Pulmonary hypertension
2	Intraoperatively	6	MI, kinked coronary artery
3	Intraoperatively	2	Prolonged CPB; abnormal orientation of PA cusps
4	Late postoperative period	51	MI, obstruction of transposed left coronary artery
5	Intraoperatively	2	MI, abnormal coronary artery
6	Early postoperative period	3	Arrhythmia

*MI indicates myocardial infarction; CPB, cardiopulmonary bypass; and PA, pulmonary artery.

four occurred in the last 18 patients included in this report. There were three intraoperative deaths: two from myocardial infarction related to unusual coronary artery anatomy and the other after prolonged cardiopulmonary bypass (>6 hours) and technical difficulty due to abnormal orientation of the pulmonary artery cusps. Two patients died during the early postoperative period due to pulmonary hypertension and intractable arrhythmia. There was one late death at 51 days after repair secondary to myocardial infarction from occlusion of the transposed left coronary artery. Three of the nonsurvivors underwent an emergency switch operation due to persistent hypoxia and acidosis despite BAS and prostaglandin E$_1$ infusion.

Functional Status

No survivor was receiving cardiac medications or diuretics at the time of the last follow-up visit (Table 3). Detailed studies consisting of echocardiography, cardiac catheterization, and 24-hour electrocardiography showed a very low incidence of postoperative sequelae, such as supravalvular pulmonary stenosis, valvular insufficiency, and symptomatic arrhythmias.

Growth and Development

Among the 27 survivors, growth and developmental follow-up was performed in 24 between 1 and 5 years of age (mean, 2.1 years). Normal growth was seen in 18 (75%) of the patients. Two patients showed poor growth with all measurements below the fifth percentile for age. One of these two patients had a diagnosis that included a ventricular septal defect and aortic coarctation in addition to the TGA that had been repaired at 8 months of age. The other growth-retarded patient had a left-sided cerebral infarct and severe neurodevelopmental delay. Six patients had head circumference below the fifth percentile, two of whom also had weight and height that were below the fifth percentile, as described above. The other four patients had weight and height appropriate for age.

Neurodevelopmental Follow-up

Results of the neurodevelopmental testing showed normal scores (≥84 or <1 SD below the mean) in 18 (75%) of the patients. Three patients were considered suspect, with scores ranging from 68 to 83 (between 1 and 2 SDs below the mean). Three had scores below 68 (>2 SDs below the mean) and were considered to be abnormal neurodevelopmentally. In two of the latter three patients, central nervous system damage was noted on head computed tomographic scans, as were persistent severe mental and psychomotor delay; one had hypotonia at the 1-year follow-up visit but had grossly normal growth and development by parental report, except for some articulation problems at 3 years of age.

Among the six patients who had head circumference below the fifth percentile, four had neurodevelopmental scores suspicious for or indicative of abnormal neurodevelopment (Table 4). Four patients had major abnormalities seen on computed tomographic scans of the head. One patient had a left-sided posterior parietal hemorrhage that was noted on follow-up computed tomography to be resolved and had normal scores on neurodevelopmental testing. Two patients had a left-sided cerebral infarct with right-sided hemiparesis and language delay on follow-up. The fourth patient had a right-sided posterior parietal hemorrhage, mental retardation, and cortical blindness. Perioperative seizures were observed in 22% of the patients identified as having normal scores on neurodevelopmental testing compared with half of those with low scores. Head circumference below the fifth percentile, abnormalities noted on head computed tomographic scans, and emergency BAS or surgery for severe hypoxia and/or metabolic acidosis were more likely to occur in patients who had low scores on neurodevelopmental testing. Table 5 lists the details of the growth and neurodevelopmental outcome of the 24 survivors of arterial switch surgery.

COMMENT

The natural history of TGA is dismal, with only 10% of affected infants surviving the first year of life.[2] Measures that improve intracardiac mixing by means of BAS, introduced by Rashkind and Miller[7] in 1966, and the use of prostaglandin E$_1$ infusion[4-6] have substantially increased short-term survival but do not allow long-term survival.

Two types of repair are advocated in the surgical management of TGA. Physiologic repair by intra-atrial rerouting of venous return was first introduced by

Senning[15] in 1959, followed later by another procedure described by Mustard[16] in 1964. Both atrial switch procedures have low operative mortality,[17-19] but the occurrence of right ventricular dysfunction, tricuspid insufficiency, venous inflow obstructions, and symptomatic arrythmias[20-21] associated with these operations complicate their long-term results and limit their acceptability. These complications could be obviated by performance of anatomic or arterial switch repair, the first successful report of which was described by Jatene et al[8] in 1975 and which since then has been used with various modifications and improving survival rate.[22-24]

Evaluation of the two management strategies for TGA should not only focus on the surgical outcome and hemodynamic results of each procedure but also consider the quality of growth and development of the survivors. Only a few of the literature reports include the growth and neurologic outcome of TGA survivors. To our knowledge, this is the first report of detailed growth and neurodevelopmental follow-up in patients who have undergone the arterial switch procedure.

Our data indicate that the majority of

Table 3.—Outcome of Arterial Switch Repair Survivors (n=24)*

Variable	No. (%)
Functional status: no cardiac medicines or diuretics	24 (100)
Growth	
Normal weight, height, HC for age	18 (75.0)
Weight, height, HC <5th percentile	2 (8.3)
Weight <5th percentile	2 (8.3)
Height <5th percentile	2 (8.3)
HC <5th percentile	6 (25.0)
Neurodevelopmental follow-up (score)	
Normal (>84)	18 (75.0)
Suspect (68-83)	3 (12.5)
Abnormal (<68)	3 (12.5)

*HC indicates head circumference.

Table 4.—Factors Associated With Low Neurodevelopmental Scores*

	No. (%)	
Factor	Normal (n=18)	Suspect/Abnormal (n=6)
HC <5th percentile†	2 (11.1)	4 (66.7)
Abnormal head CT scan†	1 (5.6)	3 (50.0)
Emergency catheterization/repair‡	2 (11.1)	3 (50.0)
Seizures	4 (22.2)	3 (50.0)

*HC indicates head circumference; CT, computed tomographic.
†*P*<.04.
‡*P*<.08.

Table 5.—Growth and Neurodevelopmental Outcome of Arterial Switch Repair Survivors*

	Follow-up Percentiles			Bayley			
Patient	Weight	Height	HC	MDI	PDI	S-B	Comment
1	45	20	**<5**	...	...	**81**	Seizures preoperatively, L hemispheric infarct, R hemiparesis, language delay
2	60	50	50	...	...	97	...
3	18	23	**<5**	...	...	**83**	Emergency catheterization
4	40	25	48	...	...	113	...
5	20	25	**<5**	125	96	...	Bradycardia, hypotension, CPR postoperatively
6	65	30	25	...	...	110	...
7	**<5**	**<5**	**<5**	**52**	**29**	...	Emergency catheterization, seizures preoperatively, L cerebral infarct, R hemiparesis, language delay
8	25	15	**<5**	**29**	**58**	...	Seizures postoperatively, R posterior parietal bleed, MR, cortical blindness
9	40	25	25	...	...	110	Seizures postoperatively, normal CT scan
10	70	78	98	130	87	...	L posterior parietal bleed, resolved
11	15	24	35	101	104	...	...
12	30	45	35	112	110	...	Seizures postoperatively, small IVH
13	58	75	50	112	111	...	...
14	8	50	20	**67**	**75**	...	Emergency repair, hypotonia
15	17	7	7	117	98	...	Emergency repair
16	95	77	20	131	111	...	...
17	**<5**	**<5**	**<5**	117	89	...	...
18	55	50	45	...	...	120	...
19	58	55	40	123	105	...	Emergency catheterization, seizures postoperatively
20	25	23	8	106	99	...	...
21	7	25	15	98	**81**	...	Increased tone in lower extremities
22	95	77	10	96	98	...	...
23	30	30	55	112	110	...	...
24	75	40	45	103	111	...	CPR×20 s in OR, seizures postoperatively

*HC indicates head circumference; MDI, Mental Developmental Index; PDI, Psychomotor Developmental Index; S-B, Stanford-Binet test; CPR, cardiopulmonary resuscitation; MR, mental retardation; CT, computed tomographic; IVH, intraventricular hemorrhage; and OR, operating room. Values in bold type are considered abnormal.

patients demonstrate normal growth and development and no impairment of cardiovascular function for up to 5 years following arterial switch repair. At least 90% of the patients were growing normally with respect to weight and height at the time of follow-up. This figure compares favorably with the 79% reported to have normal weight following the arterial switch operation (Quaegebeur et al[24]). Of concern, however, is the lack of head growth in a few of the survivors, 67% of whom have suspicious or abnormal neurodevelopmental outcome. Other factors associated with low neurodevelopmental scores include abnormal head computed tomographic scans and emergency BAS or repair. These risk factors are presumably related to the severe hypoxia and acidosis that characterize the clinical presentation of some of the patients.

At least one fourth of the survivors of arterial switch surgery demonstrate some abnormality on neurologic or developmental evaluation, although only three patients had major neurologic sequelae (hemiparesis, cortical blindness, and mental retardation). Rubay et al[25] described five of 100 patients with TGA who sustained neurologic damage, three of whom were diagnosed before the Senning operation and one of whom was diagnosed after surgery. Williams et al[26] described 10 of 115 patients with TGA who had significant neurologic damage; in five the damage was evident before the Mustard operation and in the remaining five the damage was noted immediately after repair. The inability of BAS to reliably prevent death before repair is well documented.[1,25,27] Ten to fifteen percent of patients who underwent BAS died or had a cerebrovascular accident while waiting for baffle repair.[1] The occurrence of prolonged or severe hypoxia and acidosis in patients with TGA certainly places them at increased risk for neurodevelopmental sequelae. Intraoperative factors, such as cardiopulmonary bypass, circulatory arrest, and hypothermia, may also contribute to neurologic morbidity[28-30]; however, there was no significant difference in the duration of bypass and degree of hypothermia between our patients who had normal outcome and those who had adverse outcome. Whether the type of surgical intervention itself increases the risk is unclear. There is evidence that chronic hypoxemia due to older age at the time of corrective repair of TGA by the Mustard operation may be associated with greater impairment of cognitive function.[31] Five of our patients required emergency switch operation due to progressive hypoxia and acidosis despite prostaglandin E_1 infusion and BAS. Because of the risk of major neurologic complications, early recognition, diagnosis, and intervention are mandatory. Detailed growth and neurodevelopmental follow-up, in addition to cardiac function determination, are important in the evaluation of any major cardiac surgery and should be particularly included in clinical trials that involve new procedures or techniques. It is imperative that follow-up assessment through early school age be performed in the evaluation of these procedures.

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Elevated Plasma Norepinephrine Levels in Infants of Substance-Abusing Mothers

Sally L. Davidson Ward, MD; Sally Schuetz, RN, CPNP; Laura Wachsman, MD; Xylena D. Bean, MD; Daisy Bautista; Sue Buckley; Sabitha Sehgal, MD; David Warburton, MB, MRCP

• Infants of substance-abusing mothers (ISAM) have significant growth and neurodevelopmental abnormalities. The origin of these abnormalities is unknown. We postulated that ISAM have increased sympathetic nervous system tone and altered catecholamine levels. Therefore, we measured plasma norepinephrine, epinephrine, and dopamine levels and the number and receptor affinity of β-adrenoreceptor binding sites on lymphocytes and α-adrenoreceptor binding sites on thrombocytes in 22 otherwise healthy ISAM (age, 2.1 ± 0.5 months; mean ± SD) and 15 healthy controls (age, 2.5 ± 0.8 months). Norepinephrine levels in venous blood were 1.8-fold higher in ISAM than in control infants (6.30 ± 3.85 nmol/L vs 3.55 ± 2.45 nmol/L). There were no differences in plasma epinephrine or dopamine levels. There were no differences in the number of binding sites or receptor affinity for β- and α-adrenoreceptors. We conclude that ISAM have elevated circulating norepinephrine levels compared with controls. We speculate that this is associated with increased sympathetic nervous system tone in ISAM and that the absence of adrenoreceptor down-regulation may create catecholamine suprasensitivity.

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Perinatal substance abuse among women of childbearing age has become a serious health problem in the United States. A recent survey of American households by the National Institute on Drug Abuse estimated that of 56 million women of childbearing age, 8 million, or 15%, are current abusers of illicit drugs. The same survey estimated that there are 750 000 cocaine-abusing women with children in this country.[1]

Infants of substance-abusing mothers (ISAM) have been reported to have a number of significant health problems. Infants exposed to either opiates or cocaine in utero have been reported to have lower birth weights, signs of neonatal abstinence syndrome, and abnormal scores on the Brazelton Neonatal Behavioral Assessment Scale.[2-8] In addition to growth and neurodevelopmental abnormalities, ISAM also have an increased risk for sudden infant death syndrome (SIDS)[9-13] and for having abnormalities of the ventilatory pattern during sleep recorded by pneumogram technique (overnight recordings of heart rate and ventilatory pattern).[13-16]

The mechanism by which cocaine and/or opiate exposure acts during fetal development to create abnormalities in infants is unknown. The pharmacologic action of cocaine is to block the reuptake of released monoamines (dopamine, serotonin, and norepinephrine) at the synaptic junction.[17,18] This leads to depletion of these neurotransmitters and their precursors and to catecholamine receptor suprasensitivity.[17] Animal studies of opiate exposure in utero revealed alterations in the neurochemical development of catecholaminergic systems in both central and peripheral nervous tissues of neonatal rats.[19] Opiate addiction and withdrawal alter brain catecholamine neurotransmitter and receptor function.[20,21]

Alterations in central and sympathetic nervous system neurotransmitters and receptors induced by intrauterine drug exposure could be associated with the neurodevelopmental and ventilatory pattern abnormalities in ISAM. Although direct measurements of central nervous system neurotransmitter systems cannot be made in infants, sympathetic nervous system activity can be inferred from measurements of plasma catecholamine levels.[22,23] In addition, changes in adrenoreceptor binding on circulating lymphocytes and platelets have been postulated to reflect changes in adrenoreceptors in other tissues.[24] We hypothesized that ISAM have elevated sympathetic nervous system tone, which would be reflected by alterations in circulating catecholaminergic neurotransmitters and receptors. Therefore, we measured plasma epinephrine, dopamine, and norepinephrine, α- and β-receptor binding sites, and receptor affinities on platelets and lymphocytes, respectively, in 22 ISAM and 15 healthy control infants for comparison.

PATIENTS AND METHODS

Infants of substance-abusing mothers were referred from either the state-funded clinic caring for infants born to substance-abusing mothers at Los Angeles County–University of Southern California Medical Center or from the Perinatal Substance Abuse Project at Martin Luther King, Jr, General Hospital, Los Angeles, Calif. They were identified by a positive maternal drug abuse history and/or positive urine toxicologic test at birth. Infants of substance-abusing mothers were excluded from study if they had a history of premature birth (gestation < 37 weeks based on physical assessment by Dubowitz examination[25]), required neonatal intensive care, or were requiring any medications. Assessment of gestational age was performed by two investigators (Drs Bean and Sehgal) for eight infants and was obtained by review of neonatal records for the remaining infants. They were required to be free from cardiac, pulmonary, or neurologic complications other than neonatal abstinence syndrome and to be growing appropriately. Infants who were born at term but were

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From the Division of Neonatology and Pediatric Pulmonology, Childrens Hospital of Los Angeles (Drs Ward and Warburton and Mss Bautista and Buckley); Los Angeles County–University of Southern California Medical Center (Drs Ward, Wachsman, and Warburton, and Ms Schuetz), Department of Pediatrics, University of Southern California School of Medicine (Mss Bautista and Buckley); and Martin Luther King, Jr, General Hospital, Charles R. Drew Postgraduate Medical School (Drs Bean and Sehgal), Los Angeles, Calif.

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Reprint requests to Division of Neonatology and Pediatric Pulmonology, Childrens Hospital of Los Angeles, 4650 Sunset Blvd, Bin 83, Los Angeles, CA 90027 (Dr Ward).

small for gestational age were not excluded. Records were reviewed for signs of neonatal abstinence syndrome and were scored using a system proposed by Finnegan.[26] Control infants were recruited from well-baby clinics and the general population. Control infants were required to have been full term (⩾ 37 weeks by maternal history and/or Dubowitz examination[25]), healthy and growing, without a personal or family history of apnea or a family history of SIDS, and requiring no medication. Control infants were not exposed to illicit drugs, tobacco, or excessive alcohol intake based on the history obtained from parents and/or the referring provider.

All infants were studied between 1.0 and 4.0 months of age. This age was chosen to coincide with the peak age for SIDS deaths.[27,28] Infants of substance-abusing mothers have been shown to have an increased risk for SIDS with a mean age at time of SIDS death of about 3 months.[28]

Informed consent was obtained from the caretaker of each infant studied. The study was approved by the Committee on Clinical Investigations (Institutional Review Board) at Childrens Hospital of Los Angeles.

Each infant underwent phlebotomy for 5 mL of blood from an antecubital vein as rapidly and atraumatically as possible with the infant supine. All samples were obtained between 8 and 9 AM. Four milliters of blood was placed in a tube containing ethylene glycol-bis (beta-aminoethyl ether) *N*, N^1-tetraacetic acid (EGTA) as an anticoagulant for immediate lymphocyte and thrombocyte separation and adrenergic receptor analysis. The remaining milliliters of blood were placed on ice in a tube containing EGTA as an anticoagulant and glutathione as an antioxidant for catecholamine analysis.

PREPARATION AND β-RECEPTOR BINDING ASSAY OF LYMPHOCYTES

Lymphocytes were immediately isolated from the blood using a modification of the method described by Boyum.[29] The blood was diluted with an equal volume of phosphate-buffered saline at a pH of 7.4. The mixture was layered on 3 mL of lymphocyte separation medium (Boehringer, Mannheim, West Germany). Tubes were centrifuged at 400*g* at 20°C for 40 minutes. After removal of the thrombocyte-rich plasma, the lymphocyte band was washed twice with an equal volume of phosphate-buffered saline and recentrifuged at 100*g* at 20°C for 10 minutes. The resulting pellet was resuspended in 3 mL of buffer A containing 12 mmol/L of TRIS hydrochloride, 154 mmol/L of sodium chloride , 30 mmol/L of phentolamine hydrochloride, and 0.55 mmol/L of ascorbic acid at a pH of 7.4. Phentolamine was added to inhibit α-receptor binding and ascorbic acid was added to prevent oxidation. The cells were counted and checked for viability by trypan blue staining.

β-Receptors were assayed on intact lymphocytes using a modification of the method described by Brodde et al.[30] One hundred microliters of the lymphocyte suspension (5×10^5 cells) was incubated with 50 μL of buffer A and six different concentrations of cyanopindolol labeled with iodine I 125 (^{125}I)(8140×10^{10} Bq·mmol, 5 to 200 pmol/L, New England Nuclear, Boston, Mass) for 60 minutes at 37°C. The reaction was stopped by adding 10 mL of buffer B containing 12 mmol/L of TRIS and 157 mmol/L of sodium chloride, at a pH of 7.4, at 37°C to the incubation mixture. The mixture was filtered over 25-mm glass fiber filters (Whatman GF/C, Whatman International, Maidstone, England). Each filter was rapidly washed with an additional 10 mL of buffer B. The radioactivity of the dry filters was determined using a gamma counter (Berthold LP 2101) at an efficiency of 84%.

PREPARATION AND α-RECEPTOR BINDING ASSAY OF THROMBOCYTES

The thrombocyte-rich plasma, which was obtained after removal of the lymphocyte band, was centrifuged at 1800*g* at 20°C for 10 minutes. The sedimented thrombocytes were washed three times with buffer C containing 50 mmol/L of TRIS, 100 mmol/L of sodium chloride, 0.5 mmol/L of edetic acid, and 0.8 mmol/L of ascorbic acid, at a pH of 7.5.

α-Receptors were assayed on intact thrombocytes using a modification of the method described by Motulsky et al.[31] Approximately 2×10^7 thrombocytes in 50 μL of buffer C were incubated with 100 μL of six different concentrations of tritiated yohimbine (333×10^{10} Bq·mmol, 0.5 to 25 nmol/L; New England Nuclear, Boston, Mass) for 30 minutes at 25°C. At the end of the incubation, 10 mL of buffer D containing 50 mmol/L of TRIS, 100 mmol/L of sodium chloride, and 5 mmol/L of edetic acid was added. The mixture was rapidly filtered through glass filters (Whatman GF/C 25 mm). Each filter was rapidly washed with an additional 10 mL of buffer D. The dry filters were transferred to vials containing scintillation fluid (Research Product International, 3a70), and the radioactivity was measured in a scintillation counter (Beckman LS 3H01, Irvine, Calif).

EVALUATION OF SPECIFIC BINDING

Nonspecific binding of ^{125}I-cyanopindolol and yohimbine was defined as the amount of radioactivity bound to membranes that was not displaced by high concentrations of propranolol and phentolamine, respectively. Specific binding of ^{125}I-cyanopindolol and yohimbine was defined as the total radioactivity minus nonspecific binding and amounted to 70% for ^{125}I-cyanopindolol and 65% for yohimbine. For calculation of the receptor affinity and the binding sites, the Scatchard[32] plot was used.

A linear slope ($r = .9$) was obtained in each assay, indicating one class of binding sites. The binding sites per lymphocyte or the binding sites per thrombocyte were determined by dividing the total number of receptors by the number of the appropriate cells.

CATECHOLAMINE ASSAY

One milliter of blood from the 5 mL taken for the receptor assays was drawn into specimen tubes (Vacutainer) containing EGTA as an anticoagulant and glutathione as an antioxidant (Upjohn Diagnostic, Kalamazoo, Mich). The tubes were placed on ice and were centrifuged shortly afterward. The plasma was then rapidly frozen and stored at −70°C for future analysis. Plasma dopamine, epinephrine, and norepinephrine levels were measured by radioenzymatic assay using a modification of the method described by Passon and Peuler[33] with the CAT-A-KIT (catecholamine tritiated radioenzymatic) Assay Kit (Amersham Corp, Arlington Heights, Ill).

DATA ANALYSIS

The investigator who performed all the biochemical analyses was unaware of the subject's diagnosis. All assays were performed in duplicate with an agreement within 3% for acceptability. Results are expressed as mean ± SD. The Behrens Fisher independent *t* test was used to allow for variance heteroge-

Table 1.—Comparison of Plasma Catecholamine Levels in Infants of Substance-Abusing Mothers (ISAM) and Control Infants

	ISAM	Control Infants
Norepinephrine, nmol/L (pg/mL)		
n	22	15
Mean ± SD	6.30 ± 3.85 (1065 ± 651)*	3.55 ± 2.45 (600 ± 414)
Range	1.75-16.08 (296-2721)	0.28-9.30 (48-1574)
Epinephrine, pmol/L (pg/mL)		
n	22	13
Mean ± SD	911 ± 704 (167 ± 129)	846 ± 835 (155 ± 153)
Range	213-3264 (39-598)	109-3215 (20-589)
Dopamine, pg/mL		
n	22	11
Mean ± SD	122 ± 175	88 ± 73
Range	5-833	24-251

*$P<.025$.

Table 2.—Comparison of the Number (B_{max}) of β-Receptor Binding Sites on Lymphocytes (BS/L) and α-Receptor Binding Sites on Thrombocytes (BS/T) With Respective Receptor Affinities (K_d) Between Infants of Substance-Abusing Mothers (ISAM) and Control Infants*

	ISAM	Control Infants
β-Receptors		
n	18	11
B_{max} (BS/L)	854 ± 222	846 ± 315
Range	501-1179	375-1359
K_d (pmol/L)	35 ± 14	44 ± 28
α-Receptors		
n	14	7
B_{max} (BS/T)	238 ± 34	234 ± 58
Range	172-293	159-318
K_d (pmol/L)	2.9 ± 0.9	2.3 ± 1.3
Range	1.5-4.0	1.3-4.1

*Data are expressed as number of subjects (N), mean ± SD, and range.

neity in the comparisons of age, birth weight, catecholamine levels, adrenoreceptor binding sites, and affinity constants. A χ^2 analysis was used to compare sex, socioeconomic, and racial differences between groups. Two-way analysis of variance was used to assess the impact of significant confounding variables.[34]

RESULTS

The mean (± SD) age of the control infants at the time of study was 2.5 ± 0.8 months, with a range of 1.0 to 4.0 months; seven (46%) of 15 were female. The mean age of the ISAM was 2.1 ± 0.5 months, with a range of 1.3 to 3.0 months; nine (41%) of 22 were female. The mean ages and sex distributions of the control and ISAM groups were not significantly different. Eight control infants were Hispanic, five were non-Hispanic white, one was black, and one was Asian. Seven ISAM were Hispanic, three were non-Hispanic white, and 12 were black. There was a higher proportion of black infants in the ISAM group ($P<.02$). Six control families were receiving public assistance, whereas all but one ISAM family was receiving public assistance ($P<.01$).

All infants were born at term as defined in the "Patients and Methods" section. The mean birth weight for the controls was 3297 ± 570 g, compared with 2703 ± 410 g for the ISAM group ($P<.01$). Six (27%) of the ISAM weighed between 2100 and 2500 g; one control infant weighed less than 2500 g. All infants in both groups were thriving at the time of study, with no difference in the rate of growth between the two groups; all were free of intercurrent illnesses and required no medications.

All ISAM were exposed to cocaine for either all or part of gestation (range, 3 to 9 months). Five ISAM were also exposed to opiates, two were exposed to phencyclidine, four were exposed to alcohol, and eight were exposed to tobacco. Nine ISAM had a history of positive urine toxicologic tests for cocaine at the time of birth in mother and/or baby. One ISAM had a positive methadone toxicologic test. Ten ISAM were judged to have signs of neonatal abstinence syndrome using a scoring system proposed by Finnegan.[6,26] One ISAM required chlorpromazine for symptoms of neonatal abstinence for the first 48 hours of life.

Samples for dopamine, epinephrine, and norepinephrine analyses were successfully obtained and analyzed from all 22 ISAM. Analysis was performed for β-adrenergic receptors on 18 ISAM and for α-adrenergic receptors on 14 ISAM. Samples for norepinephrine were obtained and analyzed from 15 control infants, for epinephrine from 13 infants, for dopamine from 11 infants, for β-receptors from 11 infants, and for α-receptors from seven infants.

The mean plasma norepinephrine level was 1.8-fold higher in the ISAM than in control infants ($P<.025$). There were no significant differences in the mean plasma dopamine or epinephrine levels (Table 1). There were no significant differences in the number of binding sites or receptor affinity for either β- or α-adrenergic receptors (Table 2).

The range of postnatal ages was somewhat greater for control infants than for ISAM. However, there was no significant difference in the norepinephrine levels between the 21 infants 2 months or younger (ISAM plus controls) vs the 16 infants 2 months or older (4.97 ± 2.78 nmol/L vs 5.47 ± 4.66 nmol/L, respectively). There were more black infants and infants with a birth weight of less than 2500 g in the ISAM group. However, no significant differences were revealed by comparing results between the 13 total blacks and the 24 total nonblacks (6.32 ± 3.61 nmol/L vs 4.57 ± 3.61 nmol/L) or by comparing the seven total low-birth-weight infants with the 30 higher-birth-weight infants (7.78 ± 4.74 nmol/L vs 4.58 ± 3.14 nmol/L).

Almost all ISAM (21 of 22) were receiving public assistance as compared with six of 15 controls. There were significant independent effects of both a history of maternal substance abuse ($P<.025$) and socioeconomic status ($P<.01$) on mean plasma norepinephrine levels demonstrated by two-way analysis of variance. The mean plasma norepinephrine level was 6.12 ± 3.61 nmol/L for all 27 infants requiring public assistance (ISAM plus controls) vs 2.65 ± 2.51 nmol/L for the 10 infants who did not require public assistance.

There were no differences between

ISAM who had positive vs negative urine toxicologic tests (6.53±4.24 nmol/L vs 6.10±3.47 nmol/L) or between those who experienced neonatal abstinence syndrome vs those who did not (6.53±4.31 nmol/L vs 6.93±2.83 nmol/L).

COMMENT

Perinatal substance abuse results in a number of significant consequences for the newborn, including an increased likelihood of premature birth, growth retardation, abnormalities of sleep-related respiratory control, increased incidence of SIDS, and neurodevelopmental abnormalities.[2-16,28] We have shown that ISAM between 1 and 3 months of age have an elevated mean plasma norepinephrine level. This finding is suggestive of increased sympathetic nervous system tone. This is consistent with clinical descriptions by Dixon[6] of a prolonged withdrawal syndrome in cocaine-exposed infants witnessed between 2 and 8 weeks of age.

The development of catecholaminergic neurons in the human fetus occurs between the seventh and 17th weeks of gestation.[35] This is an early-appearing system that has been hypothesized to play a role in the regulation of neural cell proliferation and differentiation and in the organization of specific neural circuitry.[36] Kellogg and Guillet[37] have hypothesized that interference with specific neurotransmitter function during fetal development could have profound consequences on subsequent brain function, although they state that precisely how a drug will influence developing neurons is difficult to predict.

The mechanism of action of cocaine is to increase neurotransmitter concentrations at the noradrenergic, serotonergic, and dopaminergic synapses by blocking reuptake. This leads to depletion of these neurotransmitters and their precursors.[17,18] With long-term cocaine exposure and neurotransmitter depletion, postsynaptic suprasensitivity develops.[17] Studies of animals following cocaine withdrawal reveal increases in brain α- and β-adrenergic and dopaminergic receptor sensitivity.[17] Opiate addiction results in an increase in the number of brain α_2- and β-adrenergic receptors.[21] Although we could not measure brain adrenergic receptor function in ISAM, changes in adrenoreceptor binding on circulating lymphocytes and platelets have been postulated to reflect changes in adrenoreceptors in other tissues.[24] Several studies have demonstrated decreases or down-regulation in lymphocyte β-adrenoreceptor binding in response to β-agonists or increased endogenous catecholamines.[38-40] We found no difference in adrenergic receptor density or affinity in ISAM despite elevated levels of circulating norepinephrine. It is possible that a lack of receptor down-regulation may enhance adrenergic activity in ISAM.

Infants from families with a lower socioeconomic status, as indicated by a requirement for public assistance, had a higher mean plasma norepinephrine level than infants with a higher socioeconomic status, independent of maternal substance abuse history. Therefore, environmental factors may be associated with alterations in sympathetic nervous system function. However, nurturing ISAM in a quiet, calm environment is the first line of treatment for neonatal abstinence syndrome.[6-8] All of the caretakers of the ISAM in this study received careful education by the hospital discharge unit and follow-up clinic in limiting environmental stimuli. Therefore, it is unlikely that the independent effect of maternal substance abuse on plasma norepinephrine levels can be explained by environmental factors. The impact of socioeconomic status and environment on sympathetic nervous system function in infants requires further study, as do the physiologic responses of ISAM to stressful environments.

Although the ISAM were thriving at the time of study, they were smaller at birth than control infants, despite being similar in estimated gestational age. We did not find a difference in catecholamine levels in the ISAM with a birth weight less than 2500 g vs ISAM with higher birth weights. However, newborn infants who are small for gestational age have been described as having a number of physiologic differences in metabolism and endocrine functions.[41] Another possible alteration in the fetal environment induced by cocaine exposure in particular is chronic hypoxia. Studies of cocaine exposure in pregnant ewes demonstrate contraction of uterine blood vessels, suggesting exposure to chronic hypoxia is present in cocaine-exposed infants.[42] Chronic hypoxia during fetal development may have contributed to our findings, as all of the ISAM in this study were exposed to cocaine. Shaul and coworkers[43] have demonstrated impaired release of catecholamines in an animal model of intrauterine growth retardation induced by fetal hypoxia. They did not, however, find a difference in baseline plasma norepinephrine levels.[43] Whether the differences in circulating norepinephrine that we have shown are a direct effect of maternal substance abuse or are secondary to an indirect effect, such as growth retardation or hypoxia, is not clear.

Infants of substance-abusing mothers are at an increased risk of dying of SIDS and have been reported to have abnormalities of their ventilatory patterns during sleep.[9-16,28] All ISAM and control infants included in this study were between 1 and 4 months of age, which coincides with the age of peak risk for SIDS.[27,28] Infants with unexplained apnea (apnea of infancy), another group of infants at increased risk for SIDS, have also been shown to have elevated levels of circulating catecholamines.[44,45] Studies of infants who have died of SIDS have shown increased concentrations of dopamine and norepinephrine in their carotid bodies at postmortem examination.[46] Both norepinephrine and dopamine have been postulated to be central respiratory inhibitors.[47-49] Norepinephrine and dopamine do not cross the blood-brain barrier, and, therefore, our findings in ISAM and the studies of infants with apnea of infancy are only relevant to the function of the sympathetic nervous system. However, the relationship between the abnormalities of sleep-related respiratory control, increased risk for SIDS, and central catecholamine neurotransmitter systems in ISAM and infants with apnea of infancy may be an important avenue for future research.

In summary, we have demonstrated a higher mean plasma norepinephrine level in a group of infants exposed to substances of abuse during fetal development. This finding is consistent with increased sympathetic nervous system tone and may be associated with the neurodevelopmental abnormalities seen in ISAM. Whether this is a direct consequence of drug exposure or is mediated via a secondary effect such as growth retardation or chronic hypoxia is not known.

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Special Contribution

Women in Medicine

Fantasies, Dreams, Myths, and Realities

Catherine DeAngelis, MD

When little girls and young women discuss their thoughts about medical careers, listeners often consider the thoughts to be fantasies. The same thoughts of little boys and young men are considered to be dreams. The difference in reactions to illusions or capricious images (fantasies) vs conceived possibilities or probabilities (dreams) has stymied the budding careers of many women. These reactions, added to the myths regarding women and men, threaten the future of the medical profession in the United States. I hope to convince you of this by reviewing the current status of women in medicine and proposing alternatives to alleviate the problem.

The gender gap in pay and occupations has narrowed during three periods of American history: the industrial revolution (1820 to 1850), the period from 1900 to 1930 in which there was a dramatic increase in white collar jobs, and now.[1] The current trend involves women entering higher-paying jobs and professions, such as business—which is the first choice of women and men—law, and medicine.

There are many indications that this trend will continue. According to the US Bureau of Labor Statistics, women have been earning more bachelor degrees than men since the mid-1980s. The current ratio is 1.1:1.0. Further, women now earn one third of all professional degrees, compared with fewer than 5% in 1960. Thirty percent of working women are professionals or managers, which is the same proportion as men. Women represent 30% of all physicians, a marked increase from the 5% between 1900 and 1960. There is every indication that this rise will continue. According to Bickel,[2] the number of women entering medical schools peaked at 12 476 in 1984 and has slightly declined since then to a level of 10 411 in 1987. On the other hand, the number of male applicants peaked in 1974 at 33 912 and has been declining dramatically since then, with 17 712 applying in 1987.

At least three major reasons account for the drastic rise of women in the general work force. First, there are more jobs available than capable men to fill them. This has been true in all fields, including science and the military. Second, the expectations of women and, to some degree, men have been elevated with advanced education and experience. Third, discrimination is decreasing, although it is still prevalent. Currently, blatant discrimination is not well tolerated in many areas, but it has been replaced by innuendo.

One example of how discrimination still exists in medicine is that while 37% of new entrants to medical schools in 1987 were women, the range was from 11% to 60%. The proportion of women in southern and north central medical schools has been consistently lower than in other schools.[3] However, the responsibility for the difference has not been determined. Is this difference a reflection of regional differences in women's attitudes regarding medicine as a career and/or the beliefs of the admissions committees?

The drastic influx of women into the medical profession has caused some anxiety and a great deal of discussion at many levels. Some of the anxiety is based on long-held myths and some on long-standing social mores. It is worthwhile to explore some of those that have had a great impact on medicine.

SCHOLARSHIP

One common myth, ie, something existing only in the imagination, is that thinking and reasoning are gender specific. Some persons act as if they actually believe in distinct testicular thoughts and ovarian ideas. Further, men generally are seen as assertive, dominant, worldly, tough, and nonemotional, while women are generally perceived as servile, gullible, weak, and emotionally labile.[4] In fact, thinking and reasoning is at most gender *related*, not gender *specific*. Crossovers are possible and desirable.

There has always been little difference between men and women in academic performance in medical school,[5] and the rate of attrition never has been significantly different.[6] While women's performances are slightly lower on standardized tests in the first 2 years of medical school, there is no significant difference in the last 2 years or during residency. Women are just as likely as men to be selected to honor societies.

Norcini et al[7] reported that women specializing in internal medicine were less likely to pass the certifying examinations, but this difference narrowed markedly to a level of 80% for women and 86% for men in 1986, the last year

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Reprint requests to The Johns Hopkins School of Medicine, Administration 106, 720 Rutland Ave, Baltimore, MD 21205 (Dr DeAngelis).

data were examined. Further, this variance has been shown to be related to age and the quality of the medical school, and proportionally there are more female than male graduates of foreign medical schools in the United States. Certifying examination data from other specialties, including pediatrics and family medicine, show little or no differences between women and men.[8,9]

Interestingly, in one study, the best predictors of men's clerkship grades were their cognitive characteristics, but noncognitive characteristics contributed more to predicting women's subsequent performance.[10] One can only conjecture about differences in the evaluators' expectations of the students.

SPECIALTY CHOICES

Women generally choose different specialties than men, with the primary care specialties predominating. For instance, 65% of pediatric residents are women and comparable figures for other specialties are 46% in obstetrics-gynecology and 41% in psychiatry. On the other hand, only 4% of surgical residents are women.[11,12] Is this a reflection of believed capabilities and/or of acceptance in these specialties?

FINANCIAL ISSUES

Generally, women graduate from medical school in more debt than men. The difference in 1987 was $3000. Further, women make less money than men in comparable positions.[13] In 1986, the median female physician's earnings were $73 100 vs $118 000 for men. However, this does represent an improvement from 1983, when the comparable figures were $57 000 and $110 000, respectively. This phenomenon is probably related to specialty choices, total number of hours worked, number of patients seen, and relative nonassertiveness in negotiating salaries.

Female physicians are less likely to be self-employed (52% vs 77%). They also see fewer patients per week (12 vs 99), but care for more new patients and spend more time with all patients. Women work fewer hours per week on average than men (52.5 vs 58.2), but recent trends show a convergence with men.[14] Also, there is less difference in hours worked with advancing age, and this difference will dissipate as the proportion of older female physicians increases.[15] Finally, physicians on average live longer than other Americans, and female physicians live 4 to 5 years longer than male physicians. It is sad that we waste so much of the extra years waiting in line to enter women's restrooms.

CHILDBEARING AND CARING

Another common myth is that making a baby is "man's work," while bearing and caring for the child is "woman's work." This particular myth is responsible, at least in part, for some interesting behaviors among male and female physicians. Approximately two thirds of female physicians are married, compared with 90% of all women and 90% of male physicians. The divorce rate is approximately 10% for female physicians, which is far lower than the national average, but double that of male physicians. Only about two thirds of married female physicians have children, compared with 90% of male physicians.[16] Further, they have fewer children and are older when they have them.[16,17] This is especially interesting because in a study conducted at the end of medical school, 85% to 90% of men and women said they wanted to have children.[18] Consider what a terrible waste of human genetic potential this represents.

Many studies and commentaries in the literature deal with maternity leave. Most have found that female physicians are at increased risk of adverse pregnancy outcome.[19-22] This increased risk probably reflects, at least in part, the long working hours and psychological stress endured by pregnant physicians.

In a study by Levinson et al,[23] the median amount of time off for pregnancy was 6 weeks post partum, with 72% of women taking no time off before delivery and 83% returning to work within 12 weeks. Interestingly, I could find nothing in the literature about the amount of time missed by male physicians because of cardiovascular or other common male health issues. We apparently react more rationally and compassionately to issues related to male biology.

Men and women have different roles in household and child caring responsibilities. For example, in a study of family practitioners, 95% to 99% of husbands of physicians worked outside the home, regardless of whether the couple had children, compared with 70% of the wives of physicians with no children and 25% of those with children.[24]

Female physicians must rely on full-time household help, day care, and relatives to provide child care.[25] Fewer than 5% of husbands of physicians take major responsibilities, compared with 50% of wives of physicians taking full responsibilities and an additional 33% making a major contribution to child care.[17,24] There are some indications that this is changing, but it is happening slowly and there is still a great deal of feeling about the subject. For example, a recent study showed that 30% of physicians felt "a significant risk to the optimal functioning of a department that hired a female of childbearing age."[26]

There can be no doubt that child care has had a profound effect on female physicians. Although pregnancies during residencies are common and usually planned, most institutions are unprepared for them.[27] Many programs have no specific maternity leave policies and I could find none with a specific plan for covering the work load of women on leave. In one recent study, no men but 44% of female physicians said they had changed career plans because of family responsibilities.[17] In another study, women said they specifically sought shorter, regular working hours because of family responsibilities.[28] While it is absolutely true that children need mothers, it is not true that the nurturing role must be totally assumed by women.

ACADEMIC PRODUCTIVITY

For the past 30 years, women have been more likely than men to enter academic medicine. However, they have not achieved the same success as men. In the only published national study that I could find, female faculty members in internal medicine were less involved in research than were men except at the professorial level. Zuckerman[29] reported that male residents publish about twice as many articles as their female counterparts. In another study, women in internal medicine had less research funding from the National Institutes of Health despite the same proportion of time reportedly devoted to research.[30] Based on my experience, I wonder if the devoted research time was eroded equally among men and women by administrative and service demands.

Also, there is evidence that education and support are different for women and that gender biases remain. For example, Beaty et al[31] found that 16% of men but 29% of women faculty members had no research training. Requests for support to attend professional development conferences were granted more often to men despite identical justification and credentials.[32] Women in internal medicine are less likely to have assigned research space.[30] Finally, when college students were asked to review articles that were identical except for the fictitious names of the authors, those with male authors were consistently rated more positively.[33] These college students might well reflect tomorrow's leaders in medicine.

ACADEMIC SUCCESS

All phases of medical practice are highly dependent on medical school, residency, and fellowship education and training. Therefore, emphasis must be placed on the academic centers, and much work is needed. While the absolute numbers and proportions of female faculty members have increased dramatically during the past two decades, there is still great discrepancy in ranks. The problem of nonpromotion appears to lie primarily at the level of the chairman rather than with the promotion committees. Interestingly, there is no association between family size and academic rank.[34]

ADMINISTRATIVE LEADERSHIP

A profound lack of female physicians in academic leadership positions exists. In 1988, two (1.6%) of 127 deans, 11% of associate deans, 22% of assistant deans, and 3% of chairpersons were women. Nine (13%) of these chairs were in pediatrics. This is a self-perpetuating problem since people are generally more comfortable in situations in which there are more than a few of a similar kind or type.[35] Also, academic leaders make the rules, and the rules must be changed.

MOLDERS, MODELS, AND MENTORS

The roles of molders, models, and mentors cannot be overemphasized. A *molder* is one who shapes. This shaping begins at birth and is greatly influenced by parents and others with whom the child has consistent contact. General social molding of a child depends a great deal on gender stereotypes. While the pace for change is increasing, a great deal of gender stereotyping exists. Gender stereotypes are still widespread and deeply ingrained in society, such as in children's books,[36] commercials,[37,38] and comic strips.[39] This is unfortunate since such stereotyping is a vehicle for discrimination against women and restricts personal fulfillment for both men and women.[40]

Models are generally persons who have skills or traits that are lacking in others and from whom one can learn by observation and comparison.[41] It is vital for female physicians to have female role models who lead successful professional and personal lives.

Mentors are generally older, more experienced professionals who sponsor, encourage, and support younger members and their career advancement.[42] It is necessary for female physicians to have female mentors. In one study, female physicians with lower-ranking female mentors received more advice and had fewer problems retaining their autonomy. However, the mentors' academic or administrative rank was the chief determinant of sponsoring effectiveness. Success was unrelated to gender.[43] This is encouraging data owing to the relative paucity of female mentors. However, data emphasize the importance of male academic leaders assuming the responsibility for being mentors (not tormentors) of promising young female physicians. This must occur at least until a "critical mass" of female mentors is available who will, it is hoped, serve long afterwards as mentors for young men as well as women.

The thought of a woman becoming a successful physician changes from a fantasy to a dream when gender stereotyping disappears. I am convinced that the most effective method of altering the gender stereotyping of a male physician is for him to have a talented daughter who wants to enter the medical profession. This whole issue would be moot within one generation if all male physicians had no sons and at least one daughter interested in medicine. Of course, this is ludicrous, and other, more rational strategies exist. I propose the following six steps:

1. For the long term, we must begin with our own children, grandchildren, and patients to engender the similarities in intellect, creativity, and general abilities in men and women. Medicine needs the talents of both.
2. For the short term, those in higher ranks (mostly men) need to be mentors for deserving women as well as men.
3. It is vitally important to have a critical mass of female leaders. To achieve this end, women must receive equal promotions, salaries, scientific training, and research space as comparable men. This requires a specific plan or program in every medical school.
4. The clock for academic training and promotions must be altered to meet the biologic needs of the human race. Childbearing is *not* a "woman's problem." It is an issue for everyone.
5. Insurance to hire people to fill in for those on maternity or illness leave must be built into every program.
6. Appropriate child-care facilities must be made available to all physicians. Again, this is *not* a woman's issue. More male physicians are becoming involved in the care of their children, and whether or not they are, the care of children affects all of us.

Most importantly, the special biologic needs of women must not be seen as *women's* issues but rather as basic human qualities of importance to both men and women. Only when highly talented women, unencumbered by unnecessary social constraints, can join the ranks of highly talented men can the success of the medical profession be ensured. Otherwise, a dwindling proportion of only half the human potential will be available to medicine.

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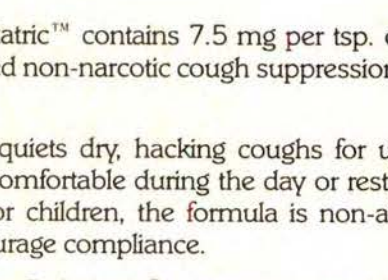

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Articles

Lumbar Puncture Frequency and Cerebrospinal Fluid Analysis in the Neonate

Jeffrey Schwersenski, MD; Lester McIntyre, MD; Charles R. Bauer, MD

• A prospective study was performed to assess the frequency and diagnostic utility of lumbar punctures in neonates both during their first week of life and thereafter. During the two 6-month periods from January 1, 1985 to June 30, 1985, and February 1, 1986 to July 31, 1986, 712 neonates underwent 728 lumbar punctures during their first week of life primarily as part of the evaluation for suspected infection, either congenital or postnatal. There were eight patients with positive spinal fluid cultures in the first week of life, but only one patient simultaneously had a positive blood culture and a clinical course consistent with meningitis. In contrast, a considerably higher yield, approximating five times that of the first week of life, was obtained in patients undergoing a lumbar puncture after the first week of life.

(*AJDC.* 1991;145:54-58)

Lumbar punctures are considered a routine part of the evaluation of neonates who are thought to exhibit signs of generalized infection. The signs of sepsis, particularly in the preterm neonate, are vague and less specific than in the term neonate or older patient. The preterm neonate is thus more likely to have a course of antibiotic treatment instituted because of clinical signs of sepsis or because of the presence of risk factors that are known to be associated with an increased incidence of sepsis. In many such cases, the lumbar puncture is often delayed because of the neonate's "unstable" condition, and antibiotic administration is begun empirically, or else the procedure is performed with the attendant risks involved. Complications of the procedure that have been described include trauma, introduction of infection, spinal epidermoid tumors, brain-stem herniation in older children, and contamination of cerebrospinal fluid (CSF) with bone marrow cells.[1-7] The use of techniques for the continuous, noninvasive monitoring of measures such as Po_2 and Pco_2 and oxygen saturation has demonstrated that significant hypoxemia occurs during handling for routine procedures, especially in sick, preterm neonates. The manipulation and positioning required for lumbar punctures have been associated with rapid clinical deterioration in neonates.[8-10]

Sepsis, with or without meningitis, is one of the more commonly encountered problems in the newborn. The incidence of systemic bacterial infection is reported to vary between one and eight per 1000 live births.[11,12] Meningitis can coexist in up to one third of neonates with sepsis. During the first month of life, the mortality for sepsis is reported to be between 10% and 30% but exceeds 30% when meningitis is superimposed. Statistically, however, the highest risk of death occurs during the first week of life, when mortality associated with infection may approach 50%.[11,12]

To evaluate the frequency and diagnostic utility of lumbar puncture and CSF analysis in the newborn, this prospective study was undertaken. The study was approved by the Subcommittee for the Protection of Human Subjects in Research at the University of Miami (Fla)/Jackson Memorial Medical Center.

PATIENTS AND METHODS

All neonates born at or transferred to the University of Miami/Jackson Memorial Medical Center who, during the two 6-month periods from January 1, 1985 to June 30, 1985, and February 1, 1986 to July 31, 1986, underwent a lumbar puncture were identified and enrolled in the study. Ventricular and shunt taps were excluded. The clinical course and treatment of the neonates were prospectively followed up. Daily records were kept of diagnoses and the results of hematologic, bacteriologic, and other significant laboratory data. Total cell counts were performed on a hemocytometer on unspun, unstained CSF specimens. Differential cell counts were performed on spun specimens, and the sediment was stained with gentian violet. The cerebrospinal fluid protein level was determined by the trichloroacetic acid method (Dupont ACA Instrument, Dupont Co, Wilmington, Del). The glucose level was measured using a glucose oxidase method (Beckman Astra Instrument, Beckman Instruments, Inc, Brea, Calif). Cerebrospinal fluid was inoculated onto thioglycolate broth, chocolate agar, 5% sheep blood agar, and an enriched 5% sheep blood agar plate. The chocolate agar plates were incubated in 4% carbon dioxide, blood agar plates were incubated aerobically, and the enriched blood agar plates were incubated anaerobically. All cultures were incubated for 72 hours before a final negative report was generated.

The neonates who underwent lumbar punctures were subclassified into two groups determined by their age at the time of the procedure: within the first week of life and thereafter.

RESULTS

During these two 6-month periods, there were a total of 11 035 admissions to the newborn services at the University of Miami/Jackson Memorial Medical Center. Of these, 826 neonates, or 7.5% of all neonatal admissions, underwent 1104 lumbar punctures. Eighty-six percent of these neonates received their lumbar punctures during the first week of life. The remaining 14%, who had their first lumbar puncture after 7 days of age, averaged slightly more than

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From the Division of Neonatology, Department of Pediatrics, University of Miami, Fla.

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Reprint requests to Department of Pediatrics (R-131), University of Miami, PO Box 016960, Miami, FL 33101 (Dr Bauer).

three lumbar punctures per patient (Table 1). Forty-three percent of the neonates studied during the first week were of low birth weight (≤2500 g), with 17.6% being of very low birth weight (≤1500 g) (Table 2). These low-birth-weight neonates not only represent those at greatest risk for sepsis but are also those in whom the chances of adverse effects due to the procedure are most likely.

Of the lumbar punctures performed during the first week of life, approximately 63% were done on the first day, with the percentage increasing to 91% within the first 72 hours (Table 2). Irrespective of age, suspected infection was the overwhelming indication for performing a lumbar puncture, accounting for 90% of the procedures in the first week of life and for 93% in those patients older than 1 week. In the group less than 1 week of age, the remaining lumbar punctures were performed predominantly because of a positive serologic test for syphilis. In those older than 1 week, posthemorrhagic hydrocephalus with raised intracranial pressure was the indication in the remaining cases (Table 3).

In the first week of life, it should be noted that an amount of CSF adequate for culture only was obtained in 103 patients, who were 14.5% of the total number of neonates studied. This was usually because of technical difficulties, which occurred most often (51.5%) in neonates of low birth weight. An additional 98 patients (13.8%) had a "bloody" CSF sample, which was defined using the criteria of Visser and Hall,[13] that is, having a red blood cell count higher than 10×10^9/L. This finding was again more frequent in the low-birth-weight neonates, accounting for 63.1% of the total cases (Table 4).

Of the total of 712 patients having a lumbar puncture performed during the first week of life, only nine CSF cultures were positive. This represents a yield (by patients) of 1.3% (Table 5). Of these nine positive cultures, six yielded *Staphylococcus epidermidis*. In all of them, this was believed to be a contaminant, as the neonates had neither cytologic results consistent with infected CSF nor a clinical course consistent with meningitis. Four of the neonates whose cultures yielded *S epidermidis* were treated with intravenous antibiotics for 3 days; the other two neonates were treated for 7 and 10 days, respectively. None of the six neonates had a simultaneously positive blood culture.

The remaining three cultures yielded *Streptococcus viridans* in one case, group B *Streptococcus* in another, and a *Bacillus* species in one of the neonates whose culture yielded *S epidermidis* 24 hours later on a repeated CSF culture. Cytologic results in two of these neonates were not consistent with an infected CSF, and simultaneous blood cul-

Table 1.—Patients Undergoing Lumbar Puncture and Age at Initial Lumbar Puncture

	Study Period 1, Jan 1 to Jun 30, 1985	Study Period 2, Feb 1 to Jul 31, 1986	Total
Total No. of admissions	5423	5612	**11 035**
No. (%) of patients undergoing lumbar puncture	355 (6.5)	471 (8.4)	**826** (7.5)
No. of lumbar punctures performed	484	620	**1104**
Age, d			
≤7			
Patients, No. (%)	298 (84)	414 (88)	**712** (86)
Lumbar punctures, No.	304	424	**728**
>7			
Patients, No. (%)	57 (16)	57 (12)	**114** (14)
Lumbar punctures, No.	180	196	**376**

Table 2.—Patients in First Week of Life by Birth Weight and by Age at Initial Lumbar Puncture*

	Study Period 1 (n=298)	Study Period 2 (n=414)	Total (n=712)
Birth weight, g			
>2500	156 (52.3)	248 (59.9)	**404** (56.7)
≤2500	142 (47.7)	166 (40.1)	**308** (43.3)
1501-2500	80 (26.8)	103 (24.9)	**183** (25.7)
≤1500	62 (20.8)	63 (15.2)	**125** (17.6)
Age, h			
0-24	175 (58.7)	273 (65.9)	**448** (62.9)
25-72	94 (31.5)	106 (25.6)	**200** (28.1)
>72	29 (9.7)	35 (8.5)	**64** (9.0)

*Values are number (percent).

Table 3.—Indications for Lumbar Puncture

		Age, d				
		≤7				>7
Indication	Study	0-24 h	25-72 h	>72 h	Total	
Suspected infection	1	170	59	23	**252**	51
	2	269	85	32	**386**	55
	Total	**439**	**144**	**55**	**638** (90%)	**106** (93%)
Positive serologic study	1	1	29	4	34	0
	2	3	18	2	23	0
	Total	**4**	**47**	**6**	**57** (8%)	**0**
Both	1	4	6	2	12	0
	2	1	3	1	5	0
	Total	**5**	**9**	**3**	**17** (2%)	**0**
Raised intracranial pressure	1	0	0	0	0	6
	2	0	0	0	0	2
	Total	**0**	**0**	**0**	**0**	**8** (7%)

Table 4.—Inadequate Specimens in First Week of Life by Birth Weight Groupings

Birth Weight Group, g	Study 1 (n=298)	Study 2 (n=414)	Total (n=712)
	Culture Only		
Total in group	**43** (14.4)	**60** (14.5)	**103** (14.5)
>2500	15 (34.9)	35 (58.3)	**50** (48.5)
≤2500	28 (65.1)	25 (41.7)	**53** (51.5)
1501-2500	11 (25.6)	15 (25)	**26** (25.2)
≤1500	17 (39.5)	10 (16.7)	**27** (26.2)
	Bloody Specimen		
Total in group	**39** (13.1)	**59** (14.3)	**98** (13.8)
>2500	13 (33.3)	33 (55.9)	**46** (46.9)
≤2500	26 (66.7)	26 (44.1)	**52** (53.1)
1501-2500	17 (43.6)	16 (27.1)	**33** (33.7)
≤1500	9 (23.1)	10 (17.0)	**19** (19.4)

Table 5.—Lumbar Puncture Yields

	Age, d					
	≤7			>7		
	Study 1	**Study 2**	**Total**	**Study 1**	**Study 2**	**Total**
No. of patients	248	414	**712**	57	57	**114**
No. of lumbar punctures	304	424	**728**	180	196	**376**
No. of positive cultures	3	6	**9**	4	4	**8**
% yield by patient	1.2	1.4	1.3	7.0	7.0	7.0
% yield by procedure	1.0	1.4	1.2	2.2	2.0	2.1
Organisms	1 group B *Streptococcus*,* 6 *Staphylococcus epidermidis*, 1 *Streptococcus viridans*, 1 *Bacillus* species			2 *S epidermidis* (1*), 1 group B *Streptococcus*,* 1 *Serratia marcescens*,* 1 *Corynebacterium* species, 1 *Acinetobacter*, 1 *Pseudomonas aeruginosa*, 1 combined *S epidermidis* and *Corynebacterium* species		

*Infants in whom both cerebrospinal fluid and blood cultures were simultaneously positive.

tures were negative. These two neonates were treated with antibiotics for 5 and 3 days, respectively. In the third neonate, group B *Streptococcus* grew in cultures from both the blood and the CSF; this patient had an increased CSF white blood cell count, a positive urine Wellcogen (latex particle agglutination for B-hemolytic *Streptococcus*), and clinical signs consistent with a central nervous system infection (Table 6).

Of the 712 neonates who underwent lumbar punctures in the first week of life, 63 (8.8%) had mothers who had been treated with antibiotics immediately preceding delivery. One of these neonates had a culture positive for *S epidermidis*, but this was thought to be a contaminant, as the cytologic study results and clinical status of the neonate were benign. All of these neonates were treated for 7 to 18 days with broad-spectum antibiotics because of the maternal indication, as well as the lack of culture reliability due to circulating maternal antibiotics.

In contrast, after the first week of life, 376 lumbar punctures were performed in 114 patients. There were eight positive CSF cultures in this group, giving a yield of 7.0%, more than five times that observed during the first week of life (Table 5). Three of these eight cultures had simultaneously positive blood cultures (group B *Streptococcus*, *Serratia marcescens*, and *S epidermidis*).

The one patient with group B streptococcal meningitis had three documented episodes of sepsis with this organism. The meningitis was associated with the second episode. The neonate with *S epidermidis* infection had a clinical and hematologic course consistent with sepsis and received a 21-day course of antibiotic therapy. The patient with *Serratia* infection died within 24 hours of the diagnosis and shortly after the initiation of treatment. Of the remaining five patients with negative blood cultures, four were considered to have contaminated specimens. The fifth patient was clinically symptomatic at the time of the positive culture and received antibiotic therapy. Symptoms and signs in this patient included seizures, apnea, and increases in both CSF white blood cell count and CSF protein level (Table 6).

COMMENT

A number of lumbar punctures are performed in most neonatal special care centers for indications such as suspected sepsis, positive serologic results, and relief of increased intracranial pressure in neonates with posthemorrhagic hydrocephalus. Often the procedure is performed by transient or junior nursery staff who may not yet fully appreciate the risks involved in performing the procedure. In addition, the procedure often provides fluid sufficient for culture only, or a blood-contaminated specimen. These problems have been reported in some series to account for up to 50% of specimens, thereby potentially reducing the amount of information that may help in reaching diagnostic and therapeutic conclusions.[13] In this study, approximately 28% of the samples obtained within the first week of life were limited by either the amount of fluid obtained or blood contamination.

We did not design the study to evaluate the risk-benefit ratio of this procedure. We did not specifically monitor neonates clinically or electronically during or after the procedure to determine their tolerance. Hence, we cannot comment on the incidence of complications in this population as compared with previously reported occurrences.

If, indeed, the co-occurrence of meningitis and sepsis in the neonate approaches 30%, the performance of a lumbar puncture as part of the complete evaluation for infection can be readily justified. In this series, however, the incidence of meningitis associated with sepsis, particularly in the first week of life, was extremely low. Even in the nine instances where positive spinal fluid cultures had been obtained in neonates who were in their first week of

Table 6.—Positive CSF Cultures*

Patient No./Gestational Age, wk/Birth Weight, g	Indication for Workup	Laboratory Results	Outcome
		Patients ≤7 d Old	
1/40/3360	Maternal temperature 39°C, 1 dose ampicillin before delivery; C section for fetal distress	CSF (culture only): *Staphylococcus epidermidis;* gastric aspirate: group B *Streptococcus;* urine Wellcogen: positive; blood culture: negative	Ampicillin sodium and gentamicin sulfate for 7 d
2/38/3170	2 cyanotic episodes after birth with opisthotonus; R/O seizures	CSF: *Bacillus* species, WBCs 3×10^6/L (100% monocytes), glucose 2.2 mmol/L, protein 0.92 g/L; CBC count: normal; urine Wellcogen: negative; blood culture: negative	Ampicillin and gentamicin for 3 d
	Repeated workup 24 h after stopping antibiotic administration	CSF: *S epidermidis,* WBCs 3×10^6/L (100% monocytes), protein 0.24 g/L, glucose QNS	Vancomycin hydrochloride for 3 d; repeated LP: WBCs 6×10^6/L, culture negative
3/43/4045	Prolonged ruptured membranes 45 h 30 min	CSF: *S epidermidis,* WBC 11×10^6/L (100% monocytes), glucose 2.5 mmol/L, protein 0.47 g/L	Ampicillin and gentamicin for 3 d
4/38/3435	Tachypnea, lethargy, opisthotonus at 24 h, R/O seizures	CSF: group B streptococcus, WBCs 689×10^6/L (27% PMNs), glucose 0.0 mmol/L, protein 2.56 g/L; urine Wellcogen: positive; blood culture: group B *Streptococcus*	Penicillin sodium for 14 d
5/40/2750	Maternal temperature 32.3°C before delivery	CSF: *S epidermidis* (broth only), RBCs $81\,000 \times 10^6$/L, WBCs 68×10^6/L	Ampicillin and gentamicin for 3 d
6/40/3760	Tachypnea, hypoxemia, acidosis at 24 h	CSF: *S epidermidis,* bloody tap; CBC count: left shift; blood culture: negative	Ampicillin and gentamicin for 10 d
7/40/3840	Maternal temperature 38.9°C before delivery	CSF: *Streptococcus viridans* (broth only), bloody tap; blood culture: negative	Ampicillin and gentamicin for 5 d; repeated CSF: WBCs 0×10^6/L, culture negative
8/40/3360	Marked tachypnea after birth, R/O pneumonia	CSF: *S epidermidis* (broth only); WBCs 1×10^6/L (100% monocytes), glucose 2.0 mmol/L, protein 0.93 g/L; urine Wellcogen: negative; blood culture: negative	Ampicillin and gentamicin for 3 d
		Patients >7 d Old	
1/31/950	1 mo old: apnea and bradycardia, abdominal distention, hypoactive; required intubation	CSF: *Serratia;* gram-negative rods; blood culture: *Serratia*	Seizures: died within 24 h; treated with oxacillin sodium, amikacin sulfate, and cefotaxime sodium
2/28/830	6 w old: apnea, pallor, bulging fontanelle; required intubation; group B *Streptococcus* sepsis at birth	CSF: group B *Streptococcus,* WBCs 349×10^6/L (14% PMNs); blood culture: group B *Streptococcus;* CBC count: neutropenia	Penicillin for 21 d
3/26/930	5 mo old; chronic lung disease, grade 4 IVH on daily LPs, increasing apnea, left shift on CBC count	CSF: *Corynebacterium* (broth only), WBCs 5×10^6/L (100% monocytes), glucose 3.4 mmol/L, protein 1.24 g/L (*Pseudomonas* grew from ET tube culture)	Oxacillin and tobramycin sulfate for 7 d; repeated CSF: culture negative
	6 mo old: asymptomatic on daily LPs	CSF: *Acinetobacter,* RBCs 162×10^6/L, WBCs 1×10^6/L (100% monocytes), glucose 4.2 mmol/L, protein 1.20 g/L	Cefotaxime sodium for 3 d; repeated CSF: culture negative
4/32/1500	2½ wk old: apnea and bradycardia, seizures; required intubation	CSF: *Pseudomonas,* WBCs 4500×10^6/L (78% monocytes), glucose 0.2 mmol/L, protein 5.41 g/L	Tobramycin for 21 d; CSF after 48 h: negative
5/27/840	28 d old: apnea and bradycardia, abdominal distention, pneumatosis of intestine	CSF: *S epidermidis* (broth only), WBCs 5×10^6/L (100% monocytes), glucose 12.0 mmol/L, protein 1.96 g/L	Ampicillin, gentamicin, and oral kanamycin sulfate for 9 d; perforated NEC; died
6/28/900	2 mo old: abdominal distention, necrotizing enterocolitis	CSF: *S epidermidis* and *Corynebacterium* (late growth), WBCs 13×10^6/L (100% monocytes), glucose 1.3 mmol/L, protein 0.26 g/L	Ampicillin, gentamicin, and oral kanamycin for 14 d
7/26/800	8 d old: lethargy, acidosis, carbon dioxide retention	CSF: *S epidermidis,* WBCs 4×10^6/L (98% monocytes), glucose 6.8 mmol/L, protein 2.31 g/L; CBC count: left shift; blood culture: *S epidermidis* and *Enterobacter*	Vancomycin hydrochloride for 21 d

*CSF indicates cerebrospinal fluid; C section, cesarean section; R/O, rule out; WBCs, white blood cells; CBC, complete blood cell; QNS, quantity not sufficient; LP, lumbar puncture; PMNs, polymorphonuclear leukocytes; RBCs, red blood cells; IVH, intraventricular hemorrhage; ET, endotracheal; and NEC, necrotizing enterocolitis.

life, eight were considered to be contaminated. None of these eight patients had simultaneously positive blood cultures, nor were they treated specifically for meningitis. After the first week of life, three neonates had simultaneously positive blood and spinal fluid cultures, accounting for a 2.5% incidence of coexisting sepsis and meningitis in this study.

Group B streptococcal sepsis is a frequently reported cause of very early neonatal sepsis that often results in significant morbidity and mortality.[14] Early-onset disease occurs in one to four per 1000 live births, the incidence and mortality being higher in smaller, premature neonates. It also has a reportedly high incidence of coexistent meningitis. In this study, only one of the lumbar punctures done in the first week of life yielded a group B *Streptococcus*, although there were 27 cases of blood culture–proved group B streptococcal sepsis in the first week, accounting for 24.3% of all positive blood cultures. In only one neonate with a positive blood culture performed after the first week of life did the culture yield group B *Streptococcus*, and this patient also had coexisting meningitis.

In summary, during two separate 6-month periods, nine of 712 patients undergoing lumbar puncture during the first week of life had positive cultures. On the other hand, eight of 114 patients undergoing lumbar puncture after the first week of life had positive cultures, most of which were clinically significant, although only three were accompanied by simultaneously positive blood cultures. This fivefold difference in incidence might be explained by the neonatal vs the maternal indication for the sepsis evaluation. The percentage of neonatal infections masked by maternal antibiotic treatment could not be determined and may have an impact on the interpretation of these data.

The results of this study suggest that the routine inclusion of lumbar puncture, performed in the first week of life as part of the workup for suspected infection in the asymptomatic but at-risk neonate, may not be indicated or justified. In contrast, when a lumbar puncture is performed for specific clinical indications in the older neonate to rule out an acquired infection, the yield is significant. The problems of blood contamination, inadequate amounts of fluid, and administration of antibiotics to the mother limit the interpretation of the results. The routine use of lumbar puncture as a part of the workup for infection during the first week of life in an asymptomatic neonate should be reassessed.

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AMA Board of Trustees Report (*JAMA.* 1990;264:2663)

Another Side Effect of NSAIDs
G. R. Gay (*JAMA.* 1990;264:2677)

*In Bronchitis and Otitis Media**

ONCE-A-DAY

SUPRAX®

cefixime/Lederle

COVERAGE[1,2] AND CONVENIENCE[3-6] NO OTHER ORAL ANTIBIOTIC CAN OFFER

- ***Broad in vitro† spectrum[1,2]***
- ***Highly active against key respiratory pathogens†[7-9]***
- ***Proven effective in clinical trials[1,10-13]***

* Due to susceptible organisms.

† Although a useful guide, *in vitro* activity may not correlate with clinical response.

SUPRAX may be administered as a single dose, once a day, or in divided doses bid if preferred.

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Please see brief summary of Prescribing Information on adjacent page.

SUPRAX® cefixime/Lederle
BRIEF SUMMARY. Please see package insert for full Prescribing Information

INDICATIONS AND USAGE

Otitis Media caused by *Haemophilus influenzae* (beta-lactamase positive and negative strains), *Moraxella (Branhamella) catarrhalis* (most of which are beta-lactamase positive), and *Streptococcus pyogenes*.*

Note: For information on otitis media caused by *Streptococcus pneumoniae*, see **CLINICAL STUDIES** section.

Acute Bronchitis and Acute Exacerbations of Chronic Bronchitis caused by *S pneumoniae* and *H influenzae* (beta-lactamase positive and negative strains).

Perform culture and susceptibility studies to determine causative organism and its susceptibility to SUPRAX. Therapy may begin while waiting for study results and may be adjusted when results are known.

Pharyngitis and Tonsillitis caused by *S pyogenes*.

Note: Penicillin is the usual drug of choice in the treatment of *S pyogenes* infections, including the prophylaxis of rheumatic fever. SUPRAX is generally effective in the eradication of *S pyogenes* from the nasopharynx; however, data establishing the efficacy of SUPRAX in the subsequent prevention of rheumatic fever are not available.

Uncomplicated Urinary Tract Infections caused by *Escherichia coli* and *Proteus mirabilis*.

*Efficacy for this organism was studied in fewer than ten patients with otitis media.

CLINICAL STUDIES

In clinical trials of otitis media in nearly 400 children between the ages of 6 months and 10 years, *S pneumoniae* was isolated from 47% of the patients, *H influenzae* from 34%, *B catarrhalis* from 15%, and *S pyogenes* from 4%.

The overall response rate of *S pneumoniae* to cefixime was approximately 10% lower and that of *H influenzae* or *B catarrhalis* approximately 7% higher (12% when beta-lactamase positive strains of *H influenzae* are included) than the response rates of these organisms to the active control drugs.

In these studies, patients were randomized and treated with either cefixime at dose regimens of 4 mg/kg bid or 8 mg/kg qd, or with a standard antibiotic regimen. Sixty-nine to 70% of the patients in each group had resolution of signs and symptoms of otitis media when evaluated two to four weeks posttreatment, but persistent effusion was found in 15% of the patients. When evaluated at the completion of therapy, 17% of patients receiving cefixime and 14% of patients receiving effective comparative drugs (18% including those patients who had *H influenzae* resistant to the control drug and who received the control antibiotic) were considered to be treatment failures. By the two- to four-week follow-up, a total of 30% to 31% of patients had evidence of either treatment failure or recurrent disease.

Bacteriological Outcome of Otitis Media at Two- to Four-Weeks Posttherapy Based on Repeat Middle Ear Fluid Culture or Extrapolation from Clinical Outcome

Organism	Cefixime(a) 4 mg/kg bid	Cefixime(a) 8 mg/kg qd	Control(a) drugs
Streptococcus pneumoniae	48/70 (69%)	18/22 (82%)	82/100 (82%)
Haemophilus influenzae beta-lactamase negative	24/34 (71%)	13/17 (76%)	23/34 (68%)
Haemophilus influenzae beta-lactamase positive	17/22 (77%)	9/12 (75%)	1/1(b)
Moraxella (Branhamella) catarrhalis	26/31 (84%)	5/5	18/24 (75%)
Streptococcus pyogenes	5/5	3/3	6/7
All Isolates	120/162 (74%)	48/59 (81%)	130/166 (78%)

(a) Number eradicated/number isolated.

(b) An additional 20 beta-lactamase positive strains of *H influenzae* were isolated, but were excluded from this analysis because they were resistant to the control antibiotic. In 19 of these the clinical course could be assessed, and a favorable outcome occurred in 10. When these cases are included in the overall bacteriological evaluation of therapy with the control drugs, 140/185 (76%) of pathogens were considered to be eradicated.

Tablets should not be substituted for suspension when treating otitis media.

CONTRAINDICATIONS

Known allergy to cephalosporins.

WARNINGS

BEFORE THERAPY WITH SUPRAX IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEPHALOSPORINS, PENICILLINS, OR OTHER DRUGS. IF THIS PRODUCT IS TO BE GIVEN TO PENICILLIN-SENSITIVE PATIENTS, CAUTION SHOULD BE EXERCISED BECAUSE CROSS-HYPERSENSITIVITY AMONG BETA-LACTAM ANTIBIOTICS HAS BEEN CLEARLY DOCUMENTED AND MAY OCCUR IN UP TO 10% OF PATIENTS WITH A HISTORY OF PENICILLIN ALLERGY. IF AN ALLERGIC REACTION TO SUPRAX OCCURS, DISCONTINUE THE DRUG. SERIOUS, ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE TREATMENT WITH EPINEPHRINE AND OTHER EMERGENCY MEASURES, INCLUDING OXYGEN, INTRAVENOUS FLUIDS, INTRAVENOUS ANTIHISTAMINES, CORTICOSTEROIDS, PRESSOR AMINES, AND AIRWAY MANAGEMENT, AS CLINICALLY INDICATED.

Administer cautiously to allergic patients.

Treatment with broad-spectrum antibiotics alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of severe antibiotic-associated diarrhea including pseudomembranous colitis. Pseudomembranous colitis has been reported with the use of SUPRAX and other broad-spectrum antibiotics (including macrolides, semisynthetic penicillins, and cephalosporins). It is important to consider this diagnosis in patients who develop diarrhea in association with antibiotic use. Symptoms of pseudomembranous colitis may occur during or after antibiotic treatment and may range in severity from mild to life threatening. Mild cases usually respond to drug discontinuation alone. Moderate-to-severe cases should be managed with fluid, electrolyte, and protein supplementation. When the colitis is not relieved by drug discontinuance, or when it is severe, oral vancomycin is the drug of choice for antibiotic-associated pseudomembranous colitis produced by *C difficile*. Other causes of colitis should be excluded.

PRECAUTIONS

General: Prolonged use may result in overgrowth of nonsusceptible organisms. If superinfection occurs, take appropriate measures.

Carefully monitor patients on dialysis. Adjust dosage of SUPRAX (cefixime) in patients with renal impairment and those undergoing continuous ambulatory peritoneal dialysis and hemodialysis. (See **DOSAGE AND ADMINISTRATION**.)

Prescribe cautiously in patients with a history of gastrointestinal disease, particularl colitis.

Drug Interactions: No significant drug interactions have been reported to date.

Drug/Laboratory Test Interactions: A false-positive reaction for ketones in the urine may occur with tests using nitroprusside but not with those using nitroferricyanide.

SUPRAX administration may result in a false-positive reaction for glucose in the urine using Clinitest®,** Benedict's solution, or Fehling's solution. Use glucose tests based on enzymatic glucose oxidase reactions (such as Clinistix®** or Tes-Tape®**).

A false-positive direct Coombs test has been reported during treatment with other cephalosporin antibiotics; therefore, it should be recognized that a positive Coombs test may be due to the drug.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Although no lifetime animal studies have been conducted to evaluate carcinogenic potential, no mutagenic potential of SUPRAX was found in standard laboratory tests. Reproductive studies revealed no fertility impairment in rats at doses up to 125 times the adult therapeutic dose.

Usage in Pregnancy: *Pregnancy Category B:* Reproduction studies have been performed in mice and rats at doses up to 400 times the human dose and have revealed no evidence of harm to the fetus due to SUPRAX.

There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery: SUPRAX has not been studied for use during labor and delivery. Treatment should only be given if clearly needed.

Nursing Mothers: It is not known whether SUPRAX is excreted in human milk. Consider discontinuing nursing temporarily during treatment with this drug.

Pediatric Use: Safety and effectiveness of SUPRAX in children aged less than 6 months have not been established.

The incidence of gastrointestinal adverse reactions, including diarrhea and loose stools, in pediatric patients receiving the suspension, was comparable to adult patients receiving tablets.

ADVERSE REACTIONS

Most adverse reactions observed in clinical trials were of a mild and transient nature. Less than four percent (3.8%) of patients in the US trials discontinued therapy because of drug-related adverse reactions. Commonly seen adverse reactions in US trials of the tablet formulation were gastrointestinal events, which were reported in 30% of adult patients on either the bid or the qd regimen. Clinically mild gastrointestinal side effects occurred in 20% of all patients, moderate events occurred in 9% of all patients, and severe adverse reactions occurred in 2% of all patients. Individual event rates included diarrhea 16%, loose or frequent stools 6%, abdominal pain 3%, nausea 7%, dyspepsia 3%, and flatulence 3%. The incidence of gastrointestinal adverse reactions, including diarrhea and loose stools, in pediatric patients receiving the suspension was comparable to adult patients receiving tablets.

Symptoms usually responded to symptomatic therapy or ceased when SUPRAX was discontinued.

Several patients developed severe diarrhea and/or documented pseudomembranous colitis, and a few required hospitalization.

The following adverse reactions have been reported following the use of SUPRAX. Incidence rates were less than 1 in 50 (less than 2%), except as noted above for gastrointestinal events.

Gastrointestinal: Diarrhea, loose stools, abdominal pain, dyspepsia, nausea, and vomiting. Several cases of documented pseudomembranous colitis were identified during the studies. The onset of pseudomembranous colitis symptoms may occur during or after therapy.

Hypersensitivity Reactions: Skin rashes, urticaria, drug fever, and pruritus. Erythema multiforme, Stevens-Johnson syndrome, and serum sickness have been reported rarely.

Hepatic: Transient elevations in SGPT, SGOT, and alkaline phosphatase.

Renal: Transient elevations in BUN or creatinine.

Central Nervous System: Headaches 3%; dizziness.

Hemic and Lymphatic Systems: Transient thrombocytopenia, leukopenia, and eosinophilia. Prolongation in prothrombin time was seen rarely.

Other: Genital pruritus, vaginitis, candidiasis.

The following adverse reactions and altered laboratory tests have been reported for cephalosporin-class antibiotics:

Adverse Reactions: Allergic reactions including anaphylaxis, toxic epidermal necrolysis, superinfection, renal dysfunction, toxic nephropathy, hepatic dysfunction, including cholestasis, aplastic anemia, hemolytic anemia, hemorrhage.

Several cephalosporins have been implicated in triggering seizures, particularly in patients with renal impairment when the dosage was not reduced (see **DOSAGE AND ADMINISTRATION** and **OVERDOSAGE**). If seizures associated with drug therapy occur, discontinue drug. Administer anticonvulsant therapy if clinically indicated.

Abnormal Laboratory Tests: Positive direct Coombs test, elevated bilirubin, elevated LDH, pancytopenia, neutropenia, agranulocytosis.

OVERDOSAGE

Gastric lavage may be indicated; otherwise, no specific antidote exists. Cefixime is not removed in significant quantities from the circulation by hemodialysis or peritoneal dialysis. Adverse reactions in small numbers of healthy adult volunteers receiving single doses up to 2 g of SUPRAX did not differ from the profile seen in patients treated at the recommended doses.

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Family History Fails to Identify Many Children With Severe Hypercholesterolemia

Thomas J. Starc, MD; Peter F. Belamarich, MD; Steven Shea, MD; Beth E. Dobrin-Seckler, RD; Ralph B. Dell, MD; Welton M. Gersony, MD; Richard J. Deckelbaum, MD

• Optimal strategies for identifying children with hypercholesterolemia have not been established. Several groups have advocated that testing of serum cholesterol levels be limited to those children who have family histories of hyperlipidemia or premature coronary heart disease. We studied the ability of comprehensive family histories to identify children with hyperlipidemia in a group of 114 children (mean age, 8 ± 4 years) who were referred for treatment of hypercholesterolemia. A positive family history was defined according to guidelines of the American Academy of Pediatrics. The mean fasting total cholesterol in the children was 5.74 ± 1.42 mmol/L (222 mg/dL). Family history was negative for hypercholesterolemia or premature coronary heart disease in 22 (22%) of 100 children with total cholesterol levels greater than the 75th percentile for their ages, in 13 (18.3%) of 71 children with total cholesterol levels greater than the 95th percentile for their ages, and in four (11.8%) of 34 children with presumed heterozygous familial hypercholesterolemia. Of the 78 children who had both hypercholesterolemia and positive family histories, hyperlipidemia was reported in 72 families, whereas premature heart disease was reported in only 27. We conclude that in a population of children referred because of known hypercholesterolemia, a detailed family history not only fails to identify many children with mild hypercholesterolemia, but also fails to identify a significant proportion of children with markedly elevated cholesterol levels. Additionally, in families of children with hypercholesterolemia, a history of hyperlipidemia is more common than a history of premature heart disease.

(*AJDC.* 1991;145:61-64)

Optimal strategies for cholesterol screening in children have not been established. Currently, both the American Academy of Pediatrics[1] and the American Heart Association[2] advocate that testing of serum cholesterol levels be limited to those children with family histories of either hyperlipidemia or premature coronary heart disease. Recently, several authors[3-7] have suggested that such limited testing may fail to identify a substantial number of children with hypercholesterolemia. There are limited data to determine if screening by family history will miss just children with mildly elevated cholesterol levels, or if it will also miss children with severe hypercholesterolemia or heterozygous familial hypercholesterolemia. Furthermore, in previous studies, family histories were usually obtained from written questionnaires completed by family members or from telephone interviews.[3-7] We do not know if a comprehensive family history, using both a questionnaire and a detailed personal interview, would identify more children with hypercholesterolemia.

Our purpose was to determine if screening recommendations based on detailed family histories would have identified children with elevated plasma cholesterol levels in a population of children referred to us with moderate to severe hypercholesterolemia. Using a selected population of children with severe hypercholesterolemia, we tested the hypothesis that currently recommended screening strategies would detect children with hypercholesterolemia.

PATIENTS AND METHODS

Setting and Subjects

The study population comprised 114 children who were referred for evaluation of hypercholesterolemia to the Children's Cardiovascular Health Center at the Columbia Presbyterian Medical Center, New York, NY, between October 1987 and March 1989. The subjects were selected from a group of 151 children referred to the center for evaluation of risk factors for atherosclerotic heart disease. Children found to have hypercholesterolemia associated with other conditions (eg, renal disease and hypothyroidism) or who were referred for other causes (eg, obesity, hypertension, and hypertriglyceridemia) were excluded from this analysis.

All children were identified by their referring physicians as having elevated plasma cholesterol levels before enrollment in our center. The original cholesterol tests were performed by the referring physicians for a variety of reasons, including family history of hyperlipidemia or early heart disease, routine cholesterol screening on all children in that pediatrician's practice, parental concern about cardiovascular disease, recommendation of the parent's physician that the child be tested, or diagnostic evaluation for some other condition.

The mean age of the children in the study was 8.4 ± 3.7 years (range, 2 to 18 years). Seventy-three percent of the children were white, 15% were Hispanic, 7% were black, and 5% were Asian. Most children were from middle- and upper-middle–class families and were referred by private pediatricians.

The mean total cholesterol of the study group prior to referral to our center was 6.74 ± 1.64 mmol/L (range, 4.53 to 12.93 mmol/L). Methods varied for obtaining the cholesterol values prior to referral to our center and included fasting, nonfasting, finger-stick, and venous blood samples.

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From the Divisions of Pediatric Cardiology (Drs Starc and Gersony) and Gastroenterology and Nutrition (Drs Belamarich, Deckelbaum, and Dell and Ms Dobrin-Seckler) of the Department of Pediatrics and the Department of Medicine and School of Public Health (Dr Shea), Children's Cardiovascular Health Center, Columbia University, College of Physicians and Surgeons, New York, NY.

Presented in part at the annual meeting of the American Heart Association, New Orleans, La, November 12, 1989.

Reprint requests to Columbia Presbyterian Medical Center, Babies Hospital, Room 102A, 630 W 168th St, New York, NY 10032 (Dr Starc).

Table 1.—Fasting Lipid Values*

	All Children (n=114)	Positive History (n=86)	Negative History (n=28)
Lipid level, mmol/L (mean±SD)			
Total cholesterol	5.74±1.44	5.94±1.53	5.11±0.80†
LDL-cholesterol	4.03±1.46	4.23±1.57	3.43±0.82†
HDL-cholesterol	1.21±0.32‡	1.21±0.33§	1.18±0.29
Triglycerides	1.17±0.64‡	1.17±0.63§	1.14±0.64

*LDL indicates low-density lipoprotein; and, HDL, high-density lipoprotein.

†$P<.02$, positive vs negative history.

‡n=113.

§n=85.

Measures

Family History.—Prior to their first visits to the center, parents were asked to answer comprehensive family history questionnaires. During the first visit, the family history was reviewed in detail with the physician and, if necessary, was completed at that time. A bilingual (Spanish-English) physician was present to assist in completion of the questionnaire when necessary. History and age of onset of myocardial infarction, coronary artery surgery, or sudden cardiac death and history of hypercholesterolemia or hypertriglyceridemia were obtained regarding each child's parents, grandparents, aunts, and uncles.

Following the recommendations of the American Academy of Pediatrics, the history of coronary heart disease was recorded as positive if a child's parent stated that a family member had a myocardial infarction, heart attack, coronary bypass surgery, or sudden cardiac death before age 50 years in men and before age 60 years in women. History of hyperlipidemia was considered positive if a parent stated that a family member had hyperlipidemia. If the family member's total cholesterol level was known and reported by the parent to be greater than 6.21 mmol/L (240 mg/dL), that family member was classified as having hypercholesterolemia regardless of whether the parent stated that the family member had hyperlipidemia.

Blood Lipids.—A fasting venous blood sample was obtained on the morning of each child's first visit to the center. Levels of plasma total cholesterol, high-density lipoprotein cholesterol (HDL-cholesterol), and triglycerides were determined using standard Lipid Research Clinics methodology[8] calibrated to Centers for Disease Control standards. Low-density lipoprotein cholesterol (LDL-cholesterol) was calculated using the following equation in which LDL-Cholesterol = [Total Cholesterol − HDL-Cholesterol − (Triglycerides/5)].[9] None of the children in the study had a triglyceride level greater than 4.52 mmol/L (400 mg/dL). One child did not undergo HDL-cholesterol testing owing to a laboratory error. Therefore, 113 HDL-cholesterol and LDL-cholesterol values were available for this analysis.

Children were classified as having hypercholesterolemia if their total cholesterol levels were greater than the 75th or the 95th percentile for their age and sex based on the "Visit 2, Random Sample" from *The Lipid Research Clinics Population Studies Data Book*.[10] We applied values from white males and females to all children because values were not published in "Visit 2, Random Sample" for blacks, Asians, or Hispanics. Because values for cholesterol distributions for 2- and 3-year-old children were also missing from the study data, we applied values for 4- to 9-year-old children to this age group. We also analyzed the data using three suggested fixed cutoff points for total cholesterol levels in children: 4.40 mmol/L (170 mg/dL),[11] 4.53 mmol/L (175 mg/dL, the approximate 75th percentile for 2- to 18-year-old children), and 5.17 mmol/L (200 mg/dL, the approximate 95th percentile for 2- to 18-year-old children).[10]

Some children have elevated total cholesterol levels because of high HDL-cholesterol levels and would be incorrectly identified as being at risk for early heart disease.[12] Therefore, we also analyzed the data using the age- and sex-specific values for LDL-cholesterol for the 75th and 95th percentiles. A subset of children was identified as having probable heterozygous familial hypercholesterolemia based on LDL-cholesterol levels of greater than 4.24 mmol/L (164 mg/dL).[13]

The HDL-cholesterol level was classified as low if it was less than or equal to the 10th percentile for age and sex based on distributions in the Lipid Research Centers' prevalence study.[10] Because values of HDL-cholesterol distributions for 2- and 3-year-old children were not among the study data, we applied values for 4- to 9-year-old children to this age group.

Statistical Analysis

Data are reported as the mean (±SD). Comparisons of lipoprotein values between those children with positive family histories and those with negative family histories were performed using Student's *t* test. We calculated the proportions of children with elevated cholesterol levels who had either positive or negative family histories. Differences in proportions were compared with the χ^2 test. Confidence intervals (CIs) for single proportions were calculated according to the method of Fleiss.[14]

RESULTS

The mean fasting total cholesterol level using Lipid Research Clinics methods in the 114 children was 5.74±1.44 mmol/L (222±56 mg/dL, range, 3.28 to 10.32 mmol/L)(Table 1). The mean LDL-cholesterol was 4.03±1.46 mmol/L (156±57 mg/dL). Both total cholesterol and LDL-cholesterol levels were higher in children with positive family histories for either premature heart disease or hyperlipidemia than in children with negative family histories for these conditions ($P<.02$) (Table 1). The HDL-cholesterol and triglyceride levels were similar in children with or without family histories of premature heart disease or hypercholesterolemia. Lipid values in children with family histories of premature ischemic heart disease were not statistically different from lipid values in children without family histories of ischemic heart disease.

Family history was negative for either hyperlipidemia or premature coronary heart disease in 22 (22%) of 100 (95% confidence interval, 14% to 30%) children with total cholesterol levels greater than the 75th percentile for their ages (Table 2). Among those children with total cholesterol levels greater than the 95th percentile for their ages, family history was negative in 13 (18.3%) of 71 (95% confidence interval, 9% to 27%) children. Similarly, family history was negative in 22 (22.9%) of 96 children with LDL-cholesterol levels greater than the 75th percentile for their ages and in 13 (20.3%) of 64 children with LDL-cholesterol levels greater than 95th percentile for their ages (Table 2).

Thirty-four children were presumed to have familial heterozygous hypercholesterolemia (LDL-cholesterol>4.24

Table 2.—Percent of Children With Negative Family Histories of Hyperlipidemia or Premature Atherosclerotic Heart Disease*

Cholesterol Levels	Total No. of Children	No. (%) With Negative History
TC ≥75th percentile	100	22 (22.0)
TC ≥95th percentile	71	13 (18.3)
TC ≥4.40 mmol/L	98	22 (22.4)
TC ≥4.53 mmol/L	95	20 (21.1)
TC ≥5.17 mmol/L	68	14 (20.6)
LDL-C ≥75th percentile	96	22 (22.9)
LDL-C ≥95th percentile	64	13 (20.3)
LDL-C ≥4.24 mmol/L	34	4 (11.8)
HDL-C ≤10th percentile	38	12 (31.6)

*TC indicates total cholesterol; LDL-C, low-density lipoprotein cholesterol; and, HDL-C, high-density lipoprotein cholesterol.

Table 3.—Family Histories in Children With Positive Family Histories and Total Cholesterol ≥75th Percentile for Age

Condition	No. (%) of Children (n = 78)
Premature myocardial event	
Parent	13 (16.7)
Grandparent	16 (20.5)
Parent or grandparent	27 (34.6)
Hyperlipidemia	
Parent	51 (65.4)
Grandparent	53 (67.9)
Parent or grandparent	72 (92.3)

mmol/L or 164 mg/dL).[13] The mean total cholesterol level in this group was 7.50±1.29 mmol/L (290±50 mg/dL). Family history was negative in four (11.8%) of 34 children with presumed familial hypercholesterolemia, compared with 18 (27.2%) of 66 children with other causes of hypercholesterolemia (*P*>.05).

Some families had more than one hypercholesterolemic child in the study. Consequently, we also analyzed the data allowing only one child per family history. Family history was negative in 21 (23.9%) of 88 families that had at least one child with a total cholesterol level greater than the 75th percentile for the child's age.

Thirty-eight (33.6%) of the 113 children tested had HDL-cholesterol levels less than or equal to the 10th percentile for their ages. Family history was negative in 12 (31.6%) of these children. Only one child with a total cholesterol level above the 75th percentile and a negative family history had a high HDL-cholesterol level and an LDL-cholesterol level that was below the 75th percentile.

There were 78 children with positive family histories and total cholesterol levels greater than the 75th percentile. Hyperlipidemia was reported in the families of 72 of these children (Table 3), while premature heart disease was reported in the families of only 27 of these children.

COMMENT

Our study differs from others[4-7] in that it examined children referred to a cardiovascular health program who had been diagnosed with moderate to severe hypercholesterolemia. Our study did not screen a normal pediatric population. Rather than developing predictive values for current cholesterol screening recommendations in the general population, our study serves as a test of the effectiveness of current cholesterol screening guidelines in a group of high-risk children.

Family history is often used as a predictor of coronary heart disease, in part because of familial aggregation of several risk factors, including hyperlipidemia, hypertension, and diabetes mellitus.[15-16] We found that current cholesterol testing recommendations based on family histories of early heart disease or hyperlipidemia would have failed to identify approximately 20% of children with moderate or severe hypercholesterolemia, 12% of children with presumed heterozygous familial hypercholesterolemia, and 31% of children with HDL-cholesterol levels less than the 10th percentile for their ages.

Despite a well-defined relationship between a family history of early heart disease and childhood hypercholesterolemia,[17-19] our data and those of others,[3-17,20,21] indicate that a family history of early heart disease or hyperlipidemia is not as accurate a predictor of hyperlipidemia in children as might be expected. In the Bogalusa Heart Study,[20] a history of paternal or maternal heart disease was not a useful marker of elevated total cholesterol levels or LDL-cholesterol levels in children. By using a positive parental history of heart disease as a marker, approximately 60% of white children and 80% of black children with elevated LDL-cholesterol levels would not have been identified.[3,20] Other studies also suggest that if a family history of heart disease or hyperlipidemia were used as a marker, 20% to 60% of hypercholesterolemic children would not be detected.[4-7,21]

Differences in methods for obtaining family histories may explain the wide discrepancy in the effectiveness of family history–based cholesterol screening that is seen between various studies.[4-5] We used both questionnaires and personal interviews by physicians to obtain our detailed family histories. Others have used written questionnaires[3-7] or a combination of written questionnaires and telephone interviews[3,7] to obtain family histories. It is likely that a more extensive family history may have contributed to a somewhat higher proportion of hypercholesterolemic children being identified in this study. Furthermore, our data indicate that a family history of hyperlipidemia more accurately predicts the presence of hypercholesterolemia in children than does a family history of premature heart disease. This may, in part, explain why studies that used a family history of heart disease as the only screening measure[3,20] identified a smaller proportion of hyperlipidemic children than studies that also used a family history of hyperlipidemia as a screening measure. However, because we studied a select group of children who had already been identified as having hypercholesterolemia, our results should not be strictly compared with findings based on studies using nonselect populations. Current guidelines[1,2] for using family histories would have failed to identify 22 hypercholesterolemic children in our study. In four of these children, the family histories of one or both parents were not known in detail. For seven of the 22 children, atherosclerotic heart disease occurred in a family member, but did not fit the standard definition of "premature." In the remaining 11 children, no particular predisposing factor could be identified.

When initially studied at our center, 14 of the 114 children who had been previously diagnosed by their pediatricians as having hypercholesterolemia had fasting total cholesterol values below the 75th percentile for their ages. Many explanations for lower total cholesterol values at the time of referral can be offered: (1) the majority of children had modified their diets prior to their first visits to our center. (2) The Lipid Research Center techniques used in our laboratory to measure blood cholesterol levels have been demonstrated to produce consistently lower cholesterol values compared with two commonly used clinical laboratory instruments, the Technicon SMAC (Technicon Instruments Corp, Tarrytown, NY) and the Du Pont Automatic Clinical Analyzer (Du Pont Co, Wilmington, Del).[22] (3) We used fasting venous blood samples in contrast to nonfasting or fingerstick samples used by some of the referring physicians. These findings emphasize the importance of using standard techniques and obtaining several cholesterol determinations prior to identifying a child as having hypercholesterolemia.

Testing strategies for detecting hypercholesterolemia in children continue to be based on consensus and expert recommendations. It was not our purpose to address the broad issues of cost effectiveness of cholesterol screening and treatment in children. However, our work, together with studies based on less strictly selected populations,[3-7] raises questions about the effectiveness of current screening policies. If it is considered beneficial to identify every child with even mild hypercholesterolemia, testing for all children should be required, and recommendations for cholesterol testing should reflect this goal. On the other hand, if screening programs should focus on identifying only high-risk individuals, more reliable screening methods will be required.

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In Other AMA Journals

ARCHIVES OF NEUROLOGY

Fetal Homotransplants (Ventral Mesencephalon and Adrenal Tissue) to the Striatum of Parkinsonian Subjects

Ignacio Madrazo, MD, DSc; Rebecca Franco-Bourland, PhD; Feggy Ostrosky-Solis, PhD; Maricarmen Aguilera, MD; Carlos Cuevas, MD; Carlos Zamorano, MD; Alfonso Morelos, MD; Eduardo Magallon, MD; Gabriel Guizar-Sahagun, MD (*Arch Neurol.* 1990;47:1281-1285)

Acute Osteomyelitis in Children

Reassessment of Etiologic Agents and Their Clinical Characteristics

Howard Faden, MD, Mauro Grossi, MD

• One hundred thirty-five children with acute osteomyelitis were identified by chart review during a 7-year period, January 1, 1980, through December 31, 1986. Bacteriologic causes were detected in 75 (55%) of the patients. *Staphylococcus aureus*, *Haemophilus influenzae* type b, and *Pseudomonos aeruginosa* were identified in 34 (25%), 16 (12%), and eight (6%) children, respectively. *Staphylococcus aureus* occurred in all age groups, *H influenzae* type b occurred only in children younger than 3 years and was the number one cause of disease in this group. *Pseudomonas aeruginosa* occurred exclusively in children older than 9 years. Children with *H influenzae* type b had clinical and laboratory findings that were almost indistinguishable from a matched group of children with osteomyelitis due to other known bacteria, although children with *H influenzae* type b tended to have more joint effusions (63% vs 27%), less lower extremity disease (22% vs 70%), and fewer positive cultures from bone or joint aspirates (41% vs 89%). Unlike most pediatric cases of osteomyelitis, the ones due to *P aeruginosa* did not represent the hematogenous route of infection; penetrating injury to the foot was present in every case. Children with *P aeruginosa* infections were older than 9 years (100%), predominantly male (88%), often afebrile (83%), and never bacteremic. These data provide guidelines for the initial work-up and management of osteomyelitis in children.

(*AJDC*. 1991;145:65-69)

Osteomyelitis continues to be a common problem in children. Although various bacteria have been identified as causal agents in osteomyelitis, *Staphylococcus aureus* has been the single most frequent identifiable cause for more than 50 years.[1-10] Scattered reports over the past 10 to 20 years have identified *Haemophilus influenzae* type b as a potential pathogen in bone infections of young children.[11-14] However, evidence for a major role of *H influenzae* type b in osteomyelitis has been lacking.[9,10]

We reviewed a 7-year experience of 135 children with acute osteomyelitis in which specific bacterial agents were identified in 75 children. *Haemophilus influenzae* type b was the cause in 16 patients and was the number one cause of disease in children younger than 3 years.

PATIENTS, MATERIALS, AND METHODS

Population

The records of all patients discharged from a children's hospital with the diagnosis of acute osteomyelitis between January 1, 1980, and December 31, 1986, were reviewed. The diagnosis of osteomyelitis must have included clear evidence of bone involvement, ie, bone lesion on plain roentgenogram or an abnormal isotopic scan, as well as evidence of infection, ie, fever, local signs, including erythema or warmth, and an elevated erythrocyte sedimentation rate (ESR). One hundred thirty-five cases were selected after exclusion of patients with previous surgical orthopedic procedures, chronic osteomyelitis, or insufficient evidence to confirm the diagnosis of acute osteomyelitis.

Data Collected

Epidemiologic and clinical data were recorded. Laboratory data included white blood cell (WBC) count; ESR; cultures of blood, bone, joint, and soft tissue; bacterial antigen (*H influenzae* type b and *Streptococcus pneumoniae*) detection; plain roentgenogram; and bone scan with technetium Tc99m pyrophosphate or gallium Ga 67.

Statistics

Student's unpaired t test, χ^2, and Fisher's Exact Test were used to analyze the data.

RESULTS

Population

One hundred thirty-five cases were evaluated. Eighty-one patients were male and 54 were female (male-female ratio = 1.5:1). Subjects ranged in age from 1 day to 22 years (mean[± SD], 5.9 ± 5.1 years). Half of the subjects were younger than 5 years. The highest occurrence rate was in the first year of life (Fig 1). One hundred six children (79%) were white, 23 (17%) were black, and six (4%) were of other races. This proportion approximately represented the racial distribution of the population in the County of Erie, New York (white, 84%; black, 13%; and other races, 3%) ($P>.05$).

Clinical Characteristics

Pain, the most common presenting complaint in 127 (94%) of the subjects, was manifested differently according to age and site of involvement (Table 1). Pain was verbalized in 88 subjects (65%), manifested by decreased range of motion in 70 subjects (52%), by limping in 47 subjects (35%), and by refusal to bear weight in 47 subjects (35%) or walk in 24 subjects (18%). One hundred fifteen children (85%) were febrile. The temperature at the time of hospital admission ranged from 36°C to 41°C (mean[± SD], 38.6°C ± 1.1°C). Local

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From the Divisions of Infectious Diseases and Hematology/Oncology, Department of Pediatrics, State University of New York, School of Medicine at Buffalo, and Children's Hospital of Buffalo (NY).

Reprint requests to Division of Infectious Diseases, Children's Hospital of Buffalo, 219 Bryant St, Buffalo, NY 14222 (Dr Faden).

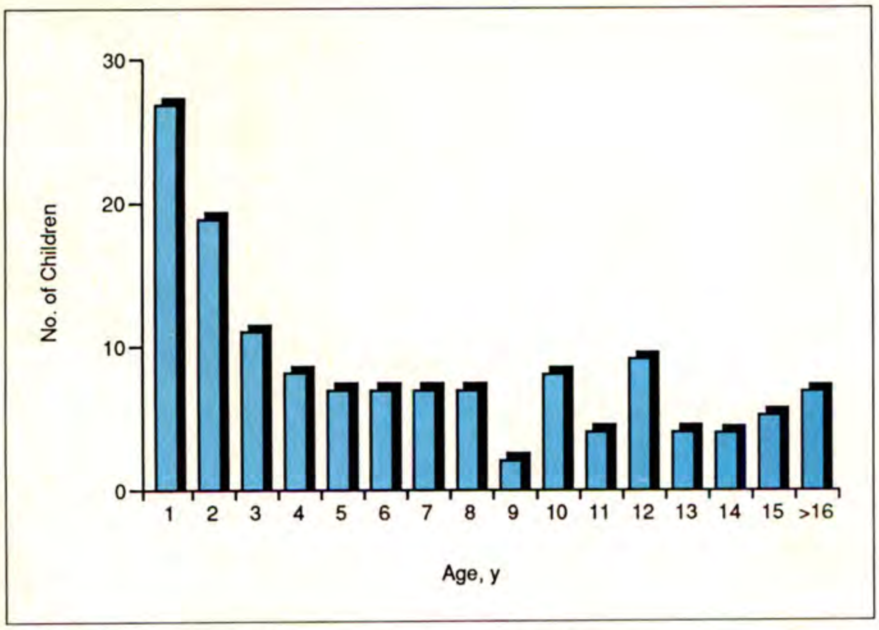

Fig 1.—Age distribution of 135 children with acute osteomyelitis.

Table 1.—Clinical Characteristics of Children With Acute Osteomyelitis

Signs and Symptoms	No. (%)
Pain	127 (94)
Fever	115 (85)
Local changes	93 (69)
Irritability	16 (12)
Anorexia	13 (10)
Lethargy	5 (4)
Vomiting	4 (3)

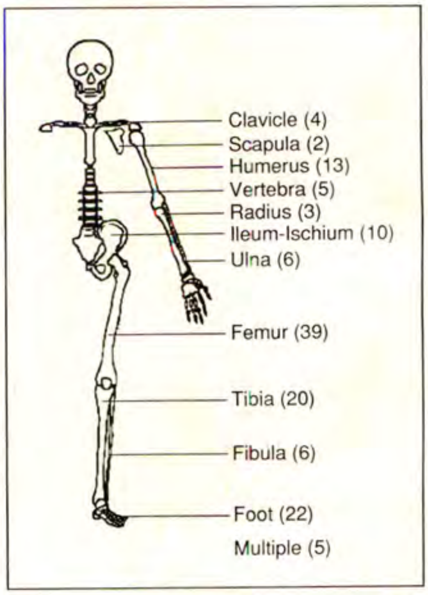

Fig 2.—Bone involvement in acute osteomyelitis.

Table 2.—Results of Bacterial Culture and Antigen Detection Assay

Test	No. Tested	No. Positive (%)
Culture		
Blood	129	39 (30)
Bone	43	22 (51)
Joint fluid	41	15 (37)
Soft tissue	6	4 (67)
Antigen detection*	44	6 (14)

*Six of 25 children younger than 24 months had positive assays.

signs and symptoms were evident in 93 children (69%).

These changes included swelling in 73 patients (54%), tenderness in 47 patients (35%), warmth in 37 patients (27%), and erythema in 35 patients (25%). Anorexia, lethargy, and vomiting were less common complaints.

The sites of infection are depicted in Fig 2. The femur was the most commonly involved bone, occurring in 39 patients, followed by the tibia in 20 patients, humerus in 13 patients, and pelvis in 10 patients. Bones of the foot were involved on 22 occasions; eight of these occurred in the calcaneous. Thus, infections of the lower extremity occurred in half of the subjects, while infections of the upper extremity occurred in less than one fifth of the subjects.

Five (3.7%) of the 135 children had infections in more than one bone. The multiple infections consisted of femur and foot in two children, humerus and clavicle, humerus and femur, and tibia and femur in one child each.

Laboratory Data

At the time of hospital admission, the WBC count was elevated in 42 patients (31%). The WBC count ranged from 2.4 to 45.5×10^9/L (mean[±SD], $13.1 \pm 6.4 \times 10^9$/L). The ESR was increased in 120 patients (89%). The ESR ranged from 4 to 132 mm/h (mean [±SD], 61±30 mm/h). Four children had both a normal WBC count and ESR at the time of hospital admission.

A causal diagnosis was sought by cultures of blood (129 patients), bone (43 patients), joint (41 patients), and soft tissue (six patients), and by determination of bacterial antigen in the urine or joint fluid (44 patients) (Table 2). Thirty-nine blood cultures (30%) were positive. Aspirates of bone, joint, and soft tissue yielded bacteria in 22 (51%), 15 (37%), and four cultures (67%), respectively. Antigen detection was positive in six samples(14%); however, the six positive results occurred in children younger than 24 months for a positive rate of 23% in infants. Overall, a bacteriologic diagnosis was confirmed in 75 (55%) of the cases.

Ten different genera of bacteria were identified as causal agents. *Staphylococcus aureus* was identified in 34 cases (25%), *H influenzae* type b was identified in 16 patients (12%), *Pseudomonas aeruginosa* was identified in eight patients (6%), group A *Streptococcus* was identified in five patients (4%), coagulase-negative *Staphylococcus* was identified in five patients (4%), and *Streptococcus pneumoniae* was identified in three patients (2%). *Escherichia coli*, *Kingella kingae*, *Neisseria meningitidis*, and group B *Streptococcus* were each isolated once. No causal agent could be identified in 60 (45%) of the subjects.

The causal agents exhibited an age-related distribution (Fig 3). Four infants younger than 30 days were infected with either *E coli*, group B *Streptococcus*, or *S aureus* (two cases). As seen in Fig 3, *S aureus* was distribut-

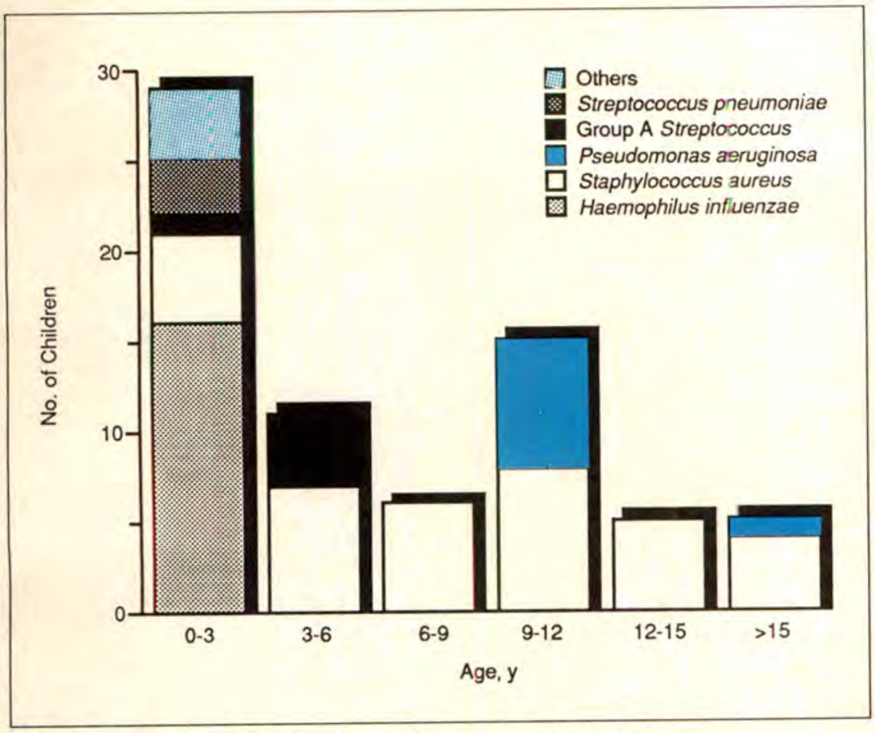

Fig 3.—Bacterial causes of acute osteomyelitis distributed by age of subject.

ed throughout the various age groups; however, *H influenzae* type b and *P aeruginosa* had rather distinctive age predilections. *Haemophilus influenzae* type b occurred only in children younger than 3 years; actually, all but one of the 16 children were younger than 2 years. However, *P aeruginosa* occurred only in children older than 9 years.

The causal agents also seemed to infect specific bony sites. For example, upper extremity osteomyelitis occurred in only 10% of the patients due to *S aureus*. In contrast, 38% the of children infected with *H influenzae* type b had upper extremity disease. In addition, *H influenzae* type b infection resulted in multiple bone involvement in three children; only five children in the entire group had multiple bone disease.

Ten children presented with osteomyelitis and obvious evidence of septic arthritis; another 36 had osteomyelitis with minimal but sufficient changes in their joints to warrant aspiration of the joint space. Joint fluids were examined in 43 of these 46 individuals and 15 (35%) proved to be infected. While 10 (29%) of 34 children with *S aureus* osteomyelitis had development of joint effusions, 10 (63%) of 16 children with *H influenzae* type b had development of joint effusions. In contrast, 60% of the staphylococcal effusions and 30% of the *Haemophilus* effusions were culture positive. Thus, 18% of children in either group had infected joints.

Roentgenographic studies were obtained on every patient. One hundred thirty-two subjects initially had plain roentgenograms. Abnormal findings were evident in 76 subjects (58%). These findings included soft-tissue swelling in 58 subjects (44%) and periosteal reaction, bony erosion, or lytic lesion in 35 subjects. Thus, 26% of the children had a bony lesion evident on presentation to the hospital. Isotopic bone scans were also performed. Of 126 technetium Tc99m pyrophosphate bone scans, 125 (99%) were abnormal. The bone scan detected osteomyelitis in 15 (94%) of 16 patients in whom the plain roentgenogram demonstrated only soft-tissue swelling. Gallium scans were also performed in 16 patient; 15 (94%) were abnormal. Every subject had at least one roentgenographic study that was consistent with osteomyelitis.

Characteristics of *H influenzae* Type b Osteomyelitis

Haemophilus influenzae type b was the second most frequent identifiable cause of osteomyelitis, comprising 21% of the identifiable organisms. All of the children were younger than 3 years (range, 5 months to 31 months; mean ± SD, 14.3 ± 7.5 months). Nine of the children with *H influenzae* type b were female and seven were male. Twelve of them were white, three were black, and one was an American Indian. All of the children were febrile at the time of hospital admission with temperatures ranging between 38.0°C and 39.9°C (mean, 38.9 ± 0.6°C). Fourteen children (89%) exhibited signs of pain. Local changes included swelling in 14 children (89%), erythema in nine children (56%), and warmth in six children (38%). One child each was irritable and lethargic. Other sites of infection were evident among 11 subjects: six had upper respiratory tract infections; two had meningitis; and three had otitis media. Of the 13 children with single bone infections due to *H influenzae* type b, six occurred in the upper extremity, three occurred in the lower extremity, and four occurred in the calcaneous. The three other children had multiple bone involvement (femur and metatarsal in two children, and femur and humerus in one child).

The WBC count was elevated in 15 (94%) of 16 children and ranged between 10 and 25.3×10^9/L (mean[±SD], $19.3 \pm 5.0 \times 10^9$/L). The ESR was abnormal in all patients. It ranged between 46 and 131 mm/h (mean[±SD], 77 ± 25 mm/h). Plain roentgenograms were abnormal in 14 (100%) of 14 children. Distinct bony lesions were seen in two (14%) of 14 children. Bone scans were abnormal in the other subjects. Blood cultures were positive in seven subjects, aspirates of bone, joint, or soft tissue were positive in five subjects, and antigen was detected in six subjects. The six positive antigen assays were the only positive tests in those six children to establish the diagnosis of *H influenzae* type b disease.

To describe the differences that might exist between *H influenzae* type b osteomyelitis and disease due to other organisms, epidemiologic, clinical, laboratory, and roentgenographic factors were compared in Table 3. A comparative group consisted of 11 children in the study who were in the same age group as those with *H influenzae* type b and

Table 3.—Characteristics of *Haemophilus influenzae* Type b Osteomyelitis Compared with Control

Characteristics*	*H influenzae* Type b (n = 16)	Control (n = 11)	*P*
Epidemiologic			
Age, mo	14.25 ± 7.5	10.6 ± 7.0	.22
Sex, M:F	7:9	6:7	.50
Race, W:B:C	12:3:1	9:2:0	.53
Clinical			
Pain	14/16	10/11	.64
Fever	16/16	10/11	.40
Local changes	15/16	7/11	.07
Joint effusion	10/16	3/11	.18
Laboratory tests			
WBC, $\times 10^9$/L	19.3 ± 5.0	19.6 ± 10.7	.90
ESR, mm/h	77 ± 25	81 ± 22	.57
Blood culture	7/16	6/11	.44
Aspirates (bone, joint, soft tissue)	5/12	8/9	.06
Bone involvement			
Extremity			
Upper	6/13	2/10	.20
Lower	3/13	7/10	.06
Foot	4/13	0/10	.08
Multiple	3/13	1/10	.40
Roentgenogram with bony lesion	2/16	4/11	.64

*W indicates white; B, black; O, other race; WBC, white blood cell count; and ESR, erythrocyte sedimentation rate.

for whom there was a definitive bacteriologic cause for the bone disease (*S aureus* in three children, *S pneumoniae* in three children, coagulase-negative staphylococci in two children, *K kingae* in one child, and *N meningitidis* in one child). As can be seen, the two groups were similar in most respects with several exceptions: joint effusions (63% vs 27%, *P* = .18) and local signs (94% vs 64%, *P* = .07) tended to occur more frequently in those with *H influenzae* type b. Cultures of aspirates from bone, joint, or soft tissue tended to be positive less often (43% vs 89%, *P* = .06) and involvement of the lower extremity occurred less often (23% vs 70%, *P* = .06) in the *H influenzae* type b group. Thus, when matched with an appropriate control group, *H influenzae* type b osteomyelitis was not unusually distinctive in most respects.

Characteristics of *P aeruginosa* Osteomyelitis

Pseudomonas aeruginosa was the third most common cause of osteomyelitis, comprising 11% of the identifiable organisms. All of the cases occurred in children older than 9 years (range, 9.2 to 17 years; mean ± SD, 10.8 ± 2.5 years) and seven of the eight children were between 9.2 and 11 years. This age group differed markedly from that seen with *H influenzae* type b and *S aureus* that occurred in children younger than 3 years and throughout all age groups, respectively. Seven of the children with *P aeruginosa* were male and one was female. Six of the children were white and two were black. All of the children had experienced penetrating injuries to the foot. Only one of the children was febrile. All of the children complained of pain. Local swelling was also evident in every subject. Local signs of erythema and warmth were present in five children (62%) and three children (37%), respectively. Seven of eight infections occurred in the foot (toe, three; calcaneous, two; and metatarsal, two).

The WBC count was rarely elevated. It ranged between 5.1 and 16.2 × 10^9/(mean, 10.3 ± 3.4 × 10^9/L). The ESR was elevated in each case and ranged between 18 and 103 mm/h (mean[± SD], 56 ± 25 mm/h). Six (75%) of eight plain roentgenograms were abnormal at the time of hospital admission. Five of the roentgenograms revealed distinct bony lesions. Bone scan were abnormal in the other two chil dren. The diagnosis was established b direct aspiration of the bone in six chil dren, soft tissue in one child, and joint i one child. Six blood cultures were ob tained; all were negative.

COMMENT

This report summarizes a 7-year experience, January 1, 1980, through December 31, 1986, with acute osteomyelitis in children. The current data, as i the past, demonstrated a high incidenc of osteomyelitis in the first few years o life. Bacteriologic diagnoses were established in 55% of the children. Th highest identification rate, 75%, resulted when blood culture and bone aspiration were used concurrently. Antigen detection was uniquely beneficial in establishing the diagnosis of *H influenzae* type b osteomyelitis. In fact, six (37.5%) of the 16 cases were confirmed by antigen detection alone. The latex agglutination test for detection of the capsular polysaccharide of *H influenzae* type b has been shown to be sensitive and when performed properly has few, if any, false-positive reactions.[15] A single report has suggested that antigen excretion in the urine may be detected by a more sensitive technique, such as enzyme-linked immunoabsorbent assay, in carriers of *H influenzae* type b.[16]

Staphylococcus aureus continued to be the major cause of osteomyelitis. It was recovered from 25% of the individuals, represented 47% of the identifiable causes of disease, and distributed throughout all age groups. Most surprising was the frequent recovery of *H influenzae* type b from the children. It was found only among children younger than 3 years and was the number one causal agent in this age group. Several studies demonstrated that *H influenzae* type b was an uncommon isolate in osteomyelitis prior to 1960.[1-6] During the subsequent 30 years, several reports identified *H influenzae* type b as a cause of osteomyelitis in children.[11-14] However, the importance of *H influenzae* type b as a major cause of osteomyelitis had not been substantiated previously.[6-8,10] Lebel and Nelson[10] reviewed a 28-year experience, 1958 through 1986, of 365 children with osteomyelitis and concluded that *H influenzae* type b caused less than 5% of all cases and 13% of the cases in children 1 to 24 months of age. In contrast, in our review of 135 cases during 7 years, 1980 through 1986, *H influenzae* type b caused 12% of all cases and 33% of the cases in children 1 to 24 months of age. The differences in the two studies cannot be readily explained except that antigen detection by latex agglutination permitted diagnosis in six (37.4%) of 16 of our patients while antigen detection by countercurrent immunoelectrophoresis, a less sensitive technique, contributed to the diagnosis in one (6.3%) of 16 patients in the Dallas study[10] ($\chi^2=2.06$, Fisher's Exact Test, $P=.15$).

In addition to the age restriction of *H influenzae* type b disease, several clinical characteristics of children with *H influenzae* type b osteomyelitis deserve mention. Earlier studies had noted a predisposition for upper extremity involvement[13,14] and a high incidence of concurrent joint disease.[9,10,13,14] Multiple bone involvement had also been observed previously.[10] Our study similarly noted a trend toward more joint effusions and upper extremity disease as well as multiple bone involvement; however, when the *H influenzae* type b group was compared with a group of children in the same age category with different bacterial causes, no statistical differences were observed.

Pseudomonas aeruginosa was the third most common etiologic agent in our series. It was isolated exclusively from children older than 9 years all of whom suffered penetrating injuries. This feature alone distinguishes *P aeruginosa* osteomyelitis from other types that predominantly represent hematogenous forms of osteomyelitis. A total of 22 cases of osteomyelitis of the foot were identified and only eight proved to be due to *P aeruginosa* (these eight were the only ones secondary to penetrating injuries of the foot). Earlier studies had documented the important role of injury as an antecedent event in *Pseudomonas* osteomyelitis.[17-20] The organism apparently resides within the sole of sneakers.[21] As observed previously, children with *P aeruginosa* osteomyelitis were likely to be male, and they were rarely febrile or bacteremic.[18]

The information generated from this study may provide guidelines to the approach and treatment of children with acute osteomyelitis. The data suggest that *S aureus* remains the most important causal agent in osteomyelitis. However, in children younger than 3 years, *H influenzae* type b is the number one concern. All cases of osteomyelitis of the foot following penetrating injuries through sneakers must be considered due to *P aeruginosa*; however, the presence of fever should cause one to think of other agents as well. The basic work-up of a child with a clinical picture of osteomyelitis should include a complete blood cell count with differential cell count, an ESR, and a blood culture. Joint fluid should be aspirated and cultured whenever available. In children younger than 3 years, urine should be checked for *H influenzae* type b capsular antigen. If these initial studies fail to yield the cause of the infection, a bone aspirate should be obtained.

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Pneumococcal Osteomyelitis and Arthritis in Children

A Hospital Series and Literature Review

Norman M. Jacobs, MD

• Twenty-nine children with pneumococcal osteomyelitis and/or arthritis, 11 of whom had osteomyelitis, were treated at Cook County Hospital, Chicago, Ill, in the past 20 years. They were mostly normal children with a single focus of infection. They represented more than 5% of the hospitalized children with a systemic pneumococcal infection. Most of the pneumococcal isolates were serotyped; serotype 19, in particular, seemed to be unusually common in these children. Twenty-three of the 29 children with pneumococcal osteomyelitis and/or arthritis had been hospitalized in the past 15 years. These 23 children were compared with 161 hospitalized children who had bone and joint infections with other isolated bacteria. The children with pneumococcal osteomyelitis and/or arthritis were indistinguishable from most of the other children, except by age. All but three of the children with pneumococcal osteomyelitis and/or arthritis were between the ages of 3 and 24 months. In this age group, *Pneumococcus* was the common isolate from children with osteomyelitis, and second only to *Haemophilus influenzae* from children with bacterial arthritis. Pneumococcal osteomyelitis and/or arthritis has never been rare; the medical literature describes at least 245 other children, most of whom were younger than 2 years.

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According to Bulkley,[1] the first patient with pneumococcal arthritis was identified in 1888, and by 1914 Bulkley could review 173 reported cases. Of these, more than one-third were children. Subsequent literature reviews of pneumococcal arthritis in 1964[2] and 1973[3] included few additional children, which suggested that pneumococcal arthritis in children had become less common. Likewise, other than the 1926 monograph on osteomyelitis by Lawford[4] and a few recent case reports,[5-7] little attention has been given to pneumococcal osteomyelitis. Thus, not surprisingly, most current pediatric textbooks say little about pneumococcal osteomyelitis and arthritis.

This article gives observations on 29 children with pneumococcal osteomyelitis and/or arthritis (PnOA), including how these children presented, how they differed from other children with bone and joint infections, and the relative prevalence of these pneumococcal infections. An attempt was made to document and review all previous reports of children with PnOA to establish the consistency of these observations.

PATIENTS AND METHODS

Patients

The children included in this article were hospitalized at Cook County Children's Hospital, Chicago, Ill, from 1967 to 1987. From 1974, the children with possible bacterial bone-joint infections and the children with other systemic bacterial infections were identified during their stay in the hospital by a member of the Pediatric Infectology Service. Before 1974, such children were identified from the records of the hospital's Microbiology Laboratory (1967 to 1974) and/or the hospital's Medical Records Department (1972 to 1974).

Comparisons

To show the relative prevalence of PnOA in the hospitalized children, these infected children were compared with two different groups of children: all other children hospitalized with a systemic pneumococcal infection (1967 to 1986) and all other children hospitalized with bacterial osteomyelitis and/or arthritis (1972 to 1987). Ages were compared using medians and semi-interquartile ranges. Medians were used because the age distributions were asymmetric, and the semi-interquartile range was used because it is a meaningful measure of variability about the median. The semi-interquartile range is equal to half of the interval from the first quartile to the third quartile of a distribution.[8]

Definitions

The children identified as having a *systemic bacterial infection* were those who had a recognized bacterial pathogen isolated from blood, bone, joint, or other normally sterile body fluid. The children identified as having *osteomyelitis* were so diagnosed by a radiologist from the roentgenograms or nuclear bone scans, or by an orthopedic surgeon after direct visualization of bone. The children identified as having *arthritis* were those who had pus drained from a joint, or those who had a systemic bacterial infection with swelling about a major joint in the absence of osteomyelitis. Children who had osteomyelitis with sterile joint effusions, obtained before antimicrobial therapy, were *not* considered to have arthritis. Excluded were children whose infections occurred in the proximity of, and following, an open wound. Thus, these children had *hematogenous* osteomyelitis and/or arthritis.

Table 1.—Children With Pneumococcal Osteomyelitis Recognized at Cook County Hospital, Chicago, Ill, 1967 to 1987

Patient/ Age/Sex	Local Disease Presentation	Culture*		Serotype	Roentgenographic Bone Site (Time, d†)
		Blood	Site		
1/7 wk/M	Elbow swelling	–	+	3	Humoral periosteum (20)
2/4 mo/F	Elbow arthritis	+	+	23	Humoral periosteum (14)
3/4 mo/F	Elbow arthritis	+	+	9	Humoral periosteum (14)
4/3 mo/M	Knee swelling	–	+	19	Tibial metaphysis (13)
5/4 mo/F	Hip arthritis	–	+	19	Femoral metaphysis (6)
6/10 mo/M	Hip arthritis	–	+	14	Femoral metaphysis (15)
7/14 y/F	Shin pain	–	+	31	Tibial metaphysis (24)
8/13 mo/F	Forearm swelling	+	ND	14	Radial diaphysis (21)
9/3 mo/M	Chest abscess	+	+	19	Sternal diaphysis (32)
10/5 mo/M	Chest abscess	ND	+	19	Costal diaphysis (6)
11/12 mo/M	Chest abscess	–	+	14	Costal diaphysis (6)

*ND indicates not done.

†Time from onset of disease until recognized bone changes.

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From the Departments of Pediatrics, Cook County Hospital and University of Illinois School of Medicine, Chicago.

Reprint requests to Department Pediatrics, Cook County Hospital, 700 S Wood St, Chicago, IL 60612 (Dr Jacobs).

The bacteria isolated were identified by the hospital laboratory by using the standard microbiologic methods in practice at the time of isolation; these methods changed over the course of the reported period. Most of the pneumococci isolated were serotyped by the quellung reaction with antiserum samples from the Statens Seruminstut, Copenhagen, Denmark.[9] Recently isolated streptococci were serogrouped with commercial latex agglutination kits; older isolates were identified presumptively by the methods recommended at that time. All *Haemophilus influenzae* isolated after 1974 were serotyped with commercial antiserum samples by slide agglutination.

Literature Review

The medical literature was reviewed by searching for all reports in English from 1915 to 1987 that identified children with PnOA; one German article[10] was also included. An attempt was made to exclude reports that duplicated the same children.

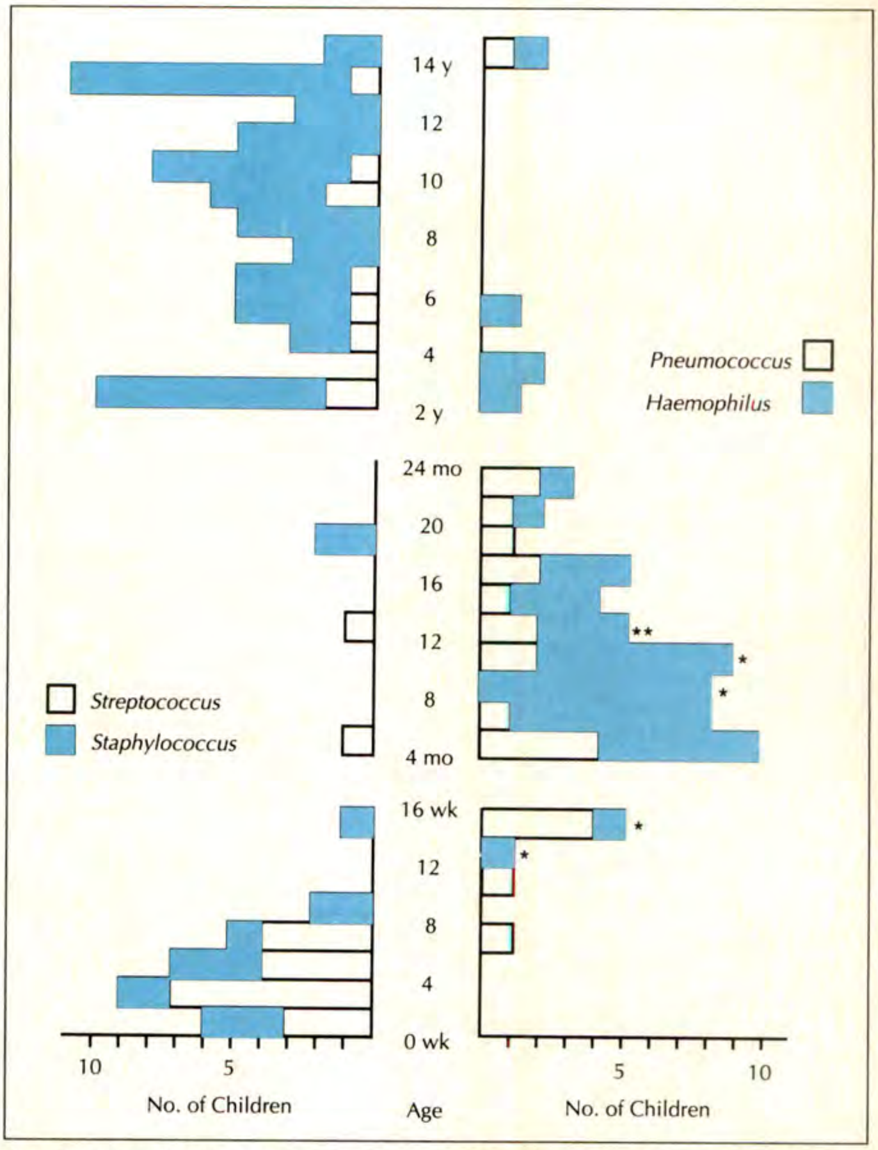
RESULTS

In the 20-year period from 1967 through 1987, twenty-nine children with PnOA were identified among children admitted to Cook County Hospital. Their ages ranged from 44 days to 14 years; 16 were male.

Pneumococcal Arthritis

Twenty-two of the children had purulent arthritis. The oldest child was aged 23 months. Nineteen of the children were apparently normal, two had histories consistent with an immunodeficiency disease (recurrent bacterial infections), and one had spherocytosis. All the children presented with fever (temperature, >38.5°C) and signs of an acutely inflamed joint. All had involvement of only a single joint: the hip (10 children), knee (five), shoulder (three), elbow (two), or ankle (two). Pus was recovered from all joints, and pneumococci were isolated from all but one joint, that of a child who had received penicillin before the joint was aspirated. He and six other children in this series had pneumococcal bacteremia; one other child had *Staphylococcus aureus* isolated from a blood culture. Two children had other sites of infection: one had meningitis and the other had pneumonia.

Pneumococcal Osteomyelitis



Age distribution of children with bacterial osteomyelitis and/or arthritis at Cook County Hospital, 1972 to 1987. Data for children with *Pneumococcus* and *Haemophilus* infections are on the right, and for those with *Streptococcus* and *Staphylococcus* infections, on the left. Asterisks indicate data for the six other children with pneumococcal osteomyelitis and/or arthritis, 1967 to 1972.

Eleven children, four with purulent arthritis and seven others, had roentgenographic osteomyelitis (Table 1). Eight of the 11 children were apparently normal. The other three had cyanotic congenital heart disease, systemic lupus erythematosus, or sickle-cell disease (patients 6 through 8, respectively, in Table 1). All 11 children also presented with fever and inflammatory signs overlying the involved bone. Three children presented with chest-wall abscesses overlying their costal or sternal osteomyelitis. Five others had destructive long-bone lesions, including a Brodie abscess in the girl with systemic lupus erythematosus. The remaining three children had only small localized periosteal reactions. The bone lesions were detected roentgenographically from 6 to 32 days after the onset of clinical signs; only four children had these changes when admitted to the hospital. Only the child with sickle-cell disease had a second site of infection; he also had pneumonia.

Systemic Pneumococcal Infections

In this 20-year period, 532 children were hospitalized with a systemic pneumococcal infection. The 29 children with PnOA accounted for more than 5% of these children. Of the remaining children, 166 had pneumonia, 137 had meningitis, 25 had another focal disease, and 175 had bacteremia with otitis media or no apparent focus.

The children with PnOA were compared with the other children with systemic pneumococcal infections, and three comparisons are of interest: their ages, the frequency they had detected bacteremia, and the serotypes of their isolated pneumococci. The age distributions of these two groups of children coincided. The median ages (± semi-interquartile ranges) of those with and those without PnOA were 11±6 and 11±8 months, respectively. The frequency of bacteremia and the isolated serotypes differed in the two groups. Bacteremia was detected in only nine (31%) of the children with PnOA but in 454 (90%) of the remaining children. Finally, two pneumococcal serotypes were more commonly isolated from the children with PnOA. Serotypes 14 and 19 were isolated from 10 (34%) and 10 (34%) of the children with PnOA, but from only 21% and 11% of the other 489 children with a serotyped isolate ($\chi^2 = 19.77$, $df = 2$, $P < .001$).

Bacterial Bone and Joint Infections

The relative prevalence of the *Pneumococcus* as a cause of bacterial osteomyelitis and/or arthritis in children was assessed for a 15-year period (1972 to 1987). In that period, 184 children were hospitalized with an established (hematogenous) bacterial osteomyelitis and/or arthritis. The *Pneumococcus* was isolated from 23 (13%) of these children. The other commonly isolated bacteria were *S aureus*, *H influenzae* type b, and *Streptococcus* groups A through C (Table 2).

Table 2.—Numbers of Children With Bacterial Osteomyelitis (OS) and/or Arthritis (AR) at Cook County Hospital, Chicago, Ill, 1972 to 1987

		All Ages			Aged 3-24 mo			
Bacterial Isolates	**Total**	**OS**	**OS+AR**	**AR**	**OS**	**OS+AR**	**AR**	**Blood Culture, No. Positive/No. Obtained**
Pneumococcus	**23**	5	4	14	3	4	13	6/20
Staphylococcus aureus	**71**	48	12	11	3	0	0	39/56
Haemophilus influenzae type b	**46**	3	2	41	3	2	35	36/43
*Streptotoccus**	**29**	9	6	14	0	0	2	9/21
Meningococcus	**5**	0	0	5	0	0	3	4/5
Other†	**10**	10	0	0	2‡	0	0	5/10
All isolates	**184**	**75**	**24**	**85**	**11**	**6**	**53**	**99/155**

**Streptococcus* groups A (11), B (17), and C (one).

†*Salmonella* (six), *Serratia* (three), and *Brucella* (one).

‡Children with sickle-cell and chronic granulomatous diseases.

Table 3.—Ages of Children With Osteomyelitis and/or Arthritis vs Ages of Their Cohorts With Other Systemic Infections at Cook County Hospital, Chicago, Ill

	Median Age±SIQR* (No. of Children)		
Infection Sites	***Pneumococcus*†**	***Haemophilus*‡**	**Group B *Streptococcus*§**
Osteomyelitis/arthritis	11±6 mo (29)	9±5 mo (46)	25±17 d (17)
Other systemic infections	11±8 mo (503)	10±7 mo (391)	21±16 d (164)
Total	... **(532)**	... **(437)**	... **(181)**

*SIQR indicates semi-interquartile range.

†Pneumococcal infections (1967 to 1987).

‡*Haemophilus influenzae* infections (1972 to 1987, excluding 20 children with epiglottitis and infants under the age of 3 days).

§Group B streptococcal infections (1972 to 1987, excluding infants under the age of 3 days).

Among the several population characteristics examined, age was the most useful predictor of the bacterial cause in these infected children. The children with pneumococcal and *Haemophilus* infections had a unimodal age distribution, with most (87%) occurring between the ages of 3 and 24 months, whereas the children with staphylococcal and streptococcal infections had a bimodal age distribution, with most (95%) occurring outside this age range (Figure). The *Pneumococcus* was isolated from 20 of the 70 children aged 3 to 24 months. In this age group, only *Haemophilus* was isolated more commonly (Table 2). However, the *Pneumococcus* was the common isolate (seven of 17 [41%]) from those with osteomyelitis. As in the children with PnOA, the age distribution of children with *Haemophilus* and group B streptococcal bone and joint infections coincided with the age distribution of their respective cohorts who had other systemic infections (Table 3).

Observations, other than age, were less useful predictors of the bacterial cause. The children's sex, clinical presentation, and peripheral blood counts were not useful. The blood culture, however, usually proved to be diagnostic. Among those children for whom a blood culture was obtained, however, only a minority of those with pneumococcal infections had detectable bacteremia. Conversely, most of the children with staphylococcal, *Haemophilus*, and meningococcal infections had detectable bacteremia (Table 2). Finally, the anatomic site of infection generally was not predictive of the bacterial cause of these infections. One exception, relative to the pneumococcal infections, was chest-wall osteomyelitis. Besides the three children with pneumococcal costal/sternal osteomyelitis noted above (Table 1), similar nonpneumococcal infections were observed in only two other children, both of whom had sickle-cell disease.

COMMENT

Since Bulkley's 1914 literature review,[1] which included 66 children under the age of 16 years, reports have noted 179 additional children with PnOA. Table 4 summarizes 16 reports[10-25] in which more than half of these children were described. Children with PnOA have been identified worldwide and in all decades since Bulkley's review. In 33 additional reports, the remaining 40 children with pneumococcal arthritis[7,26-42] and 35 with osteomyelitis[4-7,42-54] are described.

In the children in this study, pneumo-

Table 4.—Summary of 16 Hospital Reports of Osteomyelitis (OS) and/or Arthritis (AR), Including 37 Children With Pneumococcal Osteomyelitis and 67 With Pneumococcal Arthritis

				Isolate, No. of Children		
Source, y	Location	Age, y	Disease	*Staphylococcus* and/or *Streptococcus*	*Haemophilus*	*Pneumococcus*
Johnson,[11] 1921	New York, NY	<3	AR	21	3	14
Paschlau,[10] 1933	Berlin, Germany	<3	OS	41	0	9
Inge and Leibolt,[12] 1935	New York	<3	AR	9	0	2
		≥3	AR	19	0	1
Green and Shannon,[13] 1936	Boston, Mass	<2	OS	70	0	3
Self,[14] 1948	New York	All	OS	109	0	3
White and Dennison,[15] 1952	Glasgow, Scotland	All	OS	209	0	3
Samilson et al,[16] 1958	New York	<2	AR	14	2	4
		≥2	AR	12	1	1
Borella et al,[17] 1963	Memphis, Tenn	All	AR	25	6	3
Gillespie,[18] 1973	Toronto, Ontario	<3	AR	12	2	3
		≥3	AR	48	0	0
Nade,[19] 1977	Sydney, Australia	All	OS	78	3	5
		All	AR	40	14	0
Griffin and Green,[20] 1978	Boston	All	AR	38	4	9
Anderson et al,[21] 1980	Edinburgh, Scotland	All	OS	101	1	3
Fink and Nelson,[22] 1986	Dallas, Tex	<2	AR	38	133	14
		≥2	AR	112	16	3
		<2	OS	46	12	6
		≥2	OS	174	2	0
Welkon et al,[23] 1986	Philadelphia, Pa	<2	AR	9	24	8
		≥2	AR	11	4	0
Barton et al,[24] 1987	St Louis, Mo	<2	AR	14	14	3
		≥2	AR	34	6	2
LaMont et al,[25] 1987	Detroit, Mich	<2	OS	18	7	5
		≥2	OS	59	0	0

coccal bone and joint infections were found predominantly among those aged 3 to 24 months. This age group is not identifiable in most reports. Table 4 is arranged to show that most of the described children with PnOA were under the age of 2 to 3 years, and in these young children the *Pneumococcus* was a relatively common isolate. Where the age could be determined in Bulkley's review[1] and in the other reports describing children with pneumococcal arthritis[7,26-37] and pneumococcal osteomyelitis,[4-7,43-50] about two thirds of the children also were under the age of 24 months. Presumably this age association is related to the age when pneumococcal bacteremia is most common in children (Table 3).

More than 5% of the hospitalized children with systemic pneumococcal infections in this series had osteomyelitis and/or arthritis, and only two serotypes (14 and 19) accounted for 20 of these 29 infections. It is difficult to confirm either of these observations. Most reviews of serious pneumococcal infections in children are confined to those with bacteremia, and detectable bacteremia was uncommon in the untreated children with PnOA in this study. There are two reports[41,42] of children with systemic pneumococcal infections, one in 1933 and one in 1979, in which 10 (3%) and three (2%) of the children, respectively, had arthritis or osteomyelitis. Likewise, only three other described children with PnOA had their pneumococcal isolates serotyped[28,43]; none was serotype 14 or 19. However, in adults with pneumococcal arthritis,[33,55] four of 19 serotyped isolates were serotype 19. Serotype 19 also is the common isolate from children with otitis media,[56-58] an infection of a bone-lined, bone-filled cavity. Therefore, it may be that serotype 19, at least, is attracted to paraosteal tissues.

Most of the children with PnOA in this study had only a single site of infection, and most were otherwise normal children. Only three of the children had a second site of infection (pneumonia or meningitis), whereas in the preantimicrobial era, multiple infection sites were common.[1,4,11,26] However, recent cases of PnOA have been described in children compromised by malnutrition,[7] hemophilia,[35,37] immunodeficiency states,[33,49] and sickle-cell disease.[6,45,48,59] Again, only four of the children with PnOA in this study had similar problems. Sickle-cell disease, in particular, did not seem to predispose these children to PnOA. In the 20 years of the study, only one such infection was found among 40 childhood episodes of pneumococcal bacteremia occurring in 37 children with sickle-cell disease.

Differentiating the children with pneumococcal bone, joint, and deep subcutaneous infections proved to be difficult. Altering the definitions used in this report would have increased or decreased the numbers. The children presenting with pneumococcal chest-wall abscesses who proved to have costal-sternal osteomyelitis are a good example of this. This may be important because the literature review revealed that the *Pneumococcus* was the common isolate from children with costal osteomyelitis, with six other children described.[4,6,43,60,61]

CONCLUSION

The *Pneumococcus* is, and appears always to have been, a relatively common cause of bacterial osteomyelitis and/or arthritis in normal young children. The age of these children coincides with that age when pneumococcal bacteremia is most frequent. These children with PnOA may not be identified because most of them are not bacteremic when they are seen, and because many receive effective antibacterial therapy before the site of infection is cultured. Unfortunately, they are clinically indistinguishable from the children with type b *Haemophilus* arthritis, which is more common in children of the same age. As *Haemophilus* infections become less frequent because of effective vaccination, PnOA will probably become more apparent, if not more frequent.

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Influence of Otitis Media on the Correlation Between Rectal and Auditory Canal Temperatures

Thomas E. Terndrup, MD, Agnes Wong, MD

• In a noninterventional, controlled, single-blinded trial, 251 children were examined in a university hospital emergency department setting to study the influence of acute otitis media on the relationship between rectal and auditory canal temperatures. Bilateral auditory canal temperatures were measured using an infrared detection probe and microprocessor by nursing staff blinded to the presence of acute otitis media. Correlation between rectal and auditory canal temperatures in children with ($r = .81$) and without ($r = .75$) acute otitis media were not significantly different. There was no significant difference between infected (38.1°C ± 1.0°C) and uninfected ears (38.0°C ± 1.0°C) with unilateral otitis (n = 75). Although significantly higher than in uninfected children, auditory canal temperatures of children with acute otitis media reflected elevated rectal temperatures and not differences in auditory canal temperatures between ears.

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Childhood febrile illnesses account for a majority of telephone calls, unscheduled office visits, and trips to the emergency department (ED).[1,2] Fever may be the only objective indication of serious infection such as meningitis or bacteremia, particularly in infants.[3,4] Accurate determination of body temperature is essential for the differential diagnosis of acute illness. The accepted method for accurate determination of body temperature in nonneonatal ambulatory children is by inserting a thermometer into the rectum to obtain a rectal temperature (RT).[5] However, RT measurement is inconvenient, invasive, time consuming, and potentially painful; exposes personnel to contagious disease; and may lead to uncooperative behavior in some children.[6] Recent advances in thermometry technology allow body temperature to be measured as a function of infrared emissions.[7,8] Auditory canal temperature (ACT) measurement, obtained as a function of these emissions, appears to be accurate in adults and possibly in children when compared with RT obtained with standard digital electronic thermometers.[6,9-13] The use of ACT measurements would provide a noninvasive, rapid, and safe method of measuring body temperature.

Since acute otitis media (AOM) results in hyperemia, infrared emissions are increased and may influence the accuracy of ACT readings during AOM.[11] One author[14] stated that "[the ACT] . . . reading is invalidated by acute otitis media" and " . . . bilateral acute otitis media prohibits use of this method." Further, some authors have found that ACT measurements may be inaccurate in children.[10,13]

We examined the relationship between RT and bilateral ACT in children presenting for medical care in the ED. By controlling for the presence of AOM, the influence of AOM on this relationship was examined. We also sought to determine the influence of age on the accuracy of ACT measurements and the value of ACT measurements as a screening test for fever.

SUBJECTS AND METHODS

Children less than 16 years of age, who underwent either routine or physician-requested RT measurement while in the ED, were eligible for the study. Subjects were recruited by the triage or pediatric ED nurse following informed consent. The study was approved by the State University of New York Institutional Review Board for the Protection of Human Subjects. This study was carried out from November 16 through December 3, 1989.

Subjects underwent RT measurement with a calibrated digital electronic thermometer (Diatek, San Diego, Calif) and bilateral ACT measurement using an infrared emission detection probe and microprocessor (First Temp, Intelligent Medical Systems, Carlsbad, Calif). Rectal temperatures were obtained in the monitor mode, allowing at least 3 minutes for equilibration. Participating pediatric ED nurses were given a brief inservice on the use of the probe and microprocessor. They were instructed to retract the external ear posteriorly and place the probe snugly into the ostia of each auditory canal. Digital readings were obtained after approximately 2 seconds. Physicians, pediatric residents, or pediatric ED attending physicians then evaluated and treated each patient in the standard fashion, "blinded" to ACT measurements.

Following patient discharge, the physician recorded the presence or absence of AOM based on the presence of three or more of the following criteria: (1) rapid onset of fever and/or ear pain and/or irritability, (2) bulging or full tympanic membrane, (3) opaque or erythematous tympanic membrane, (4) limited or no mobility of tympanic membrane.[15] Auditory canal temperature readings of patients who could not be adequately evaluated were eliminated from analysis.

Temperature calibrations of the digital electronic thermometer, performed against a water bath, were found to be accurate within ±0.1°C (SD) at the beginning and end of the experimental period. The probe and microprocessor have an internal, self-adjusting calibration system and were operated in the rectal mode.

The relationship between RT and ACT for all patients was described using linear regression. The difference between RT and

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From the Departments of Pediatrics (Drs Terndrup and Wong) and Critical Care and Emergency Medicine (Dr Terndrup), State University of New York Health Science Center at Syracuse.

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Reprint requests to Critical Care and Emergency Medicine, SUNY Health Science Center, 750 E Adams St, Syracuse, NY 13210 (Dr Terndrup).

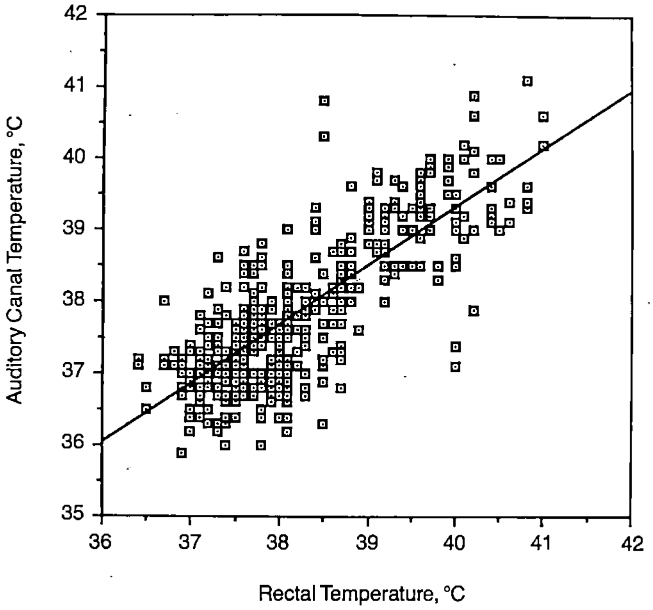

Fig 1.—Scattergram of 496 pairs of rectal and auditory canal temperatures.

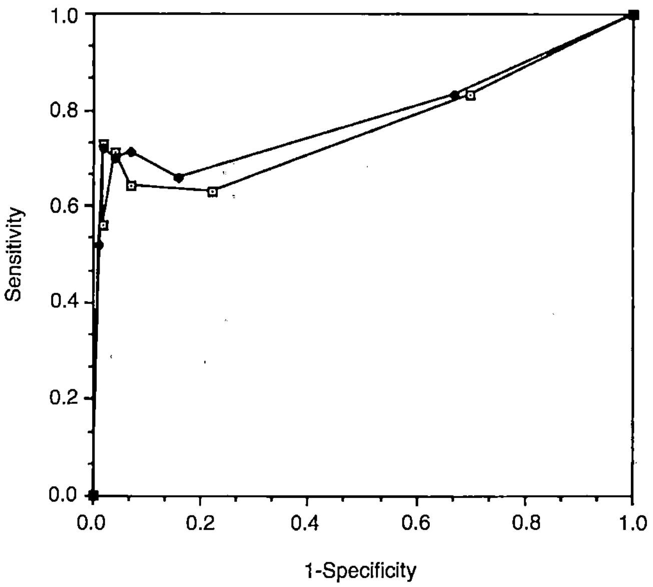

Fig 2.—Receiver operating characteristic curves for right (squares) and left (diamonds) auditory canal temperatures compared with rectal temperatures using five cutoffs for fever.

Table 1.—Influence of Otitis Media on Rectal and Auditory Canal Temperatures*

	Otitis Media	**No Otitis Media**	**P**
No. of ears	176	320	...
Age, mo	18.5±14.1	23.1±25.0	<.05
Temperature,°C			
Rectal	38.5±1.0	38.0±0.9	<.05
Tympanic	38.2±1.1	37.6±0.9	<.05
Rectal minus tympanic	0.3±0.6	0.4±0.6	NS
γ	.81	.75	NS†

*Data are means±SDs and Pearson correlation coefficient. NS indicates not significant.
†z test for homogeneity of correlation coefficient.

ACT was assessed using the two-tailed Student *t* test for all subjects, subjects with or without AOM, and for patients with unilateral AOM. Significant differences in the correlation between RT and ACT for ears with and without AOM were examined by calculating a *Z* value for homogeneity of the Pearson correlation coefficient. Significance was considered to be achieved at $P<.05$.

RESULTS

During the 2-week study period, 251 subjects were evaluated. Six patients whose ACTs could not be fully evaluated for the criteria of AOM were eliminated. Patients were young (mean age ±SD, 21.4±22 months), with 53% being male. Rectal temperature (mean±SD, 38.2°C±0.9°C; range, 36.4°C to 41°C) was significantly higher than ACT (37.8°C±1.0°C; range, 35.9°C to 41°C) for all subjects. Acute otitis media was seen in 35.5% (176/496) of ears. Using linear regression, the relationship between RT and ACT is described as follows: ACT=0.811(RT)+6.836 (Fig 1).

Rectal temperature was significantly greater than ACT in patients with and without AOM (Table 1). The correlation between RT and ACT was not significantly different for patients with ($r=.81$) and without ($r=.75$) AOM. Both the mean ACTs and RTs were greater in patients with AOM than in those without AOM. Patients with unilateral AOM (n=75) had no significant difference in the ACT of infected ears (38.1°C±1.0°C) vs uninfected ears (38.0°C±1.0°C), reflecting elevated body temperature and no unilateral ACT elevation in patients with AOM.

To examine the effectiveness of the device in fever screening, sensitivity, specificity, positive predictive values, and negative predictive values were calculated at four different RT readings (Table 2). By plotting sensitivity vs 1-specificity, a receiver operating characteristic curve is constructed (Fig 2). The receiver operating characteristic curve shows the relationship of sensitivity and specificity for a given ACT as a predictor of RT, using various cutoff points for fever. By choosing the point on the receiver operating characteristic curve that is farthest from the line of equivalence between X and Y values (ie, 39.0°C), the greatest value of the ACT test for fever screening information is obtained. Using an ACT of greater than or equal to 39.0°C to define fever, the sensitivity is found to be 73%, and the specificity is 98% (Table 2). Using an ACT of greater than or equal to 38.0°C to define fever, the sensitivity is found to be 68% and specificity is 93%.

Age less than 29 months had little influence on the relationship between ACT and RT(Table 3). The correlation between ACT and RT is not significantly different for age groups below 29 nths. There is a significant reduction the correlation coefficient for subcts older than 29 months compared th the group younger than 29 months <.05; *Z* test for homogeneity of the arson correlation coefficient).

COMMENT

The results of this study suggest that OM does not significantly alter the re-tionship between RT and ACT in am-ulatory children. Although children ith infected ears had significantly gher temperatures than children with ninfected ears, this reflected elevated dy temperature and not differences in CTs between ears. In patients with ilateral AOM, there was no signifi-nt difference between the ACT of the fected vs the uninfected ear. The ele-ation of ACT during AOM was due to creased body temperature and not ue to the effects of local inflammation. sing ACT measurements for fever reening is specific but not sensitive nough to allow for reliable screening. he accuracy of ACT readings was sig-ificantly poorer for active toddlers mpared with younger ED patients.

Other investigators have performed limited comparisons between RT and ACT measurement during AOM in children. Lobbes,[16] in an unblinded trial, studied 30 children with unilateral AOM and 30 uninfected control subjects. She found that an ear with AOM was significantly warmer than the contralateral healthy ear, with a mean difference of 0.1°C (0.26°F). No significant differences between ears were seen in controls. She concluded that the increased ACT measurement reflected the effects of the local inflammation and might serve as a predictor of AOM. Weir and Weir[11] found in an unblinded, uncontrolled study of 62 children with unilateral AOM that infected ears were an average of 0.09°C ± 0.4°C warmer than uninfected ears. The results of this study support the conclusion that the differences between the ACTs of infected and uninfected ears is not large enough to interfere with the accuracy of the probe and microprocessor used to estimate body temperature in patients with AOM.

Other authors have examined the relationship between RT and ACT measurements with the use of the probe and microprocessor in children. Treloar and Muma[10] compared the relationship between axillary temperature, ACT, and RT in 224 children younger than 3 years of age in the ED. They found that AOM did not significantly change the relationship between the ACT and RT. The correlation between the RT and ACT was high overall ($r = .81$) but was lower for temperatures less than 38.0°C ($r = .12$) and greater than 39.5°C ($r = .24$). The overall specificity was 100%, but the sensitivity was only 54%. Ros[18] studied the correlation between temperatures measured with glass mercury thermometers and ACTs in 102 ambulatory children. He found that the mean (±SD) difference between the two methods was 0.3°C ± 0.7°C, which is nearly identical to our study. However, both oral temperatures and RTs were compared with ACT readings (no calibration of thermometers is mentioned) and inadequate equilibration times were used with the mercury thermometers for oral temperature measurement, making his results difficult to interpret.

Our study found that the age of the patients influenced the correlation between the RT and the ACT. For patients younger than 29 months of age, there was no difference in the correlation coefficients. However, there was a significant reduction in the correlation coefficient for patients older than 29 months of age. This difference may reflect the difficulty in positioning the auditory canal probe in active, less compliant toddlers. One group showed that there was a poor correlation in young patients less than 2 months of age.[10] They attributed this to the smaller size of the external auditory canal relative to the size of the temperature probe. By

Table 2.—Fever Screening Using Different Rectal Temperature Cutoffs*

Rectal temperature cutoff, °C	≥37.5	≥38.0	≥38.5	≥39.0	≥39.5
Sensitivity, %	65	68	71	73	54
Specificity, %	81	93	96	98	99
Positive predictive value, %	93	89	84	91	84
Negative predictive value, %	37	78	88	94	94
Prevalence, %	81	48	31	20	13

*Sensitivity = true positive/(true positive + false negative); specificity = true negative/(true negative + lse positive); positive predictive value = true positive/(true positive + false positive); and negative redictive value = true negative/(true negative + false negative).

Table 3.—Influence of Age on the Relationship Between Rectal and Auditory Canal Temperatures*

Age range, mo	0-3	4-6	7-12	13-18	19-28	29-42	43-180
No. of Patients, %	26	34	47	36	42	38	28
Otitis media, %	15	40	51	36	35	38	24
Male, %	46	62	47	44	57	58	54
Temperature, °C							
Rectal	38.1 ± .6	38.5 ± 1.2	38.2 ± .9	38.4 ± 1	38.2 ± .9	38.0 ± .9	38.0 ± .7
Tympanic	37.4 ± .7	38.1 ± 1.1	37.8 ± 1	38.0 ± 1	38.0 ± .9	37.6 ± .8	37.5 ± .8
Rectal minus tympanic	0.4 ± .4	0.4 ± .6	0.4 ± .6	0.4 ± .6	0.3 ± .5	0.3 ± .8	0.4 ± .7
r	.81	.86	.83	.82	.84	.59	.57

*Data are the percent of patients in each age group with acute otitis media, means ± SDs, and Pearson correlation coefficient.

slightly retracting the external ear and orienting the probe anteriorly, the impact of smaller size may have been overcome in this study.

The infrared tympanic thermometer has also been studied in various clinical situations in adults. Shinozaki et al[9] performed 260 comparisons of ACTs with RTs and pulmonary artery vascular temperature in adult patients who underwent postoperative coronary artery bypass surgery. Over a broad temperature range (34°C to 39.5°C), the correlation between the ACTs and the pulmonary artery temperatures was excellent ($r = .98$). Terndrup et al[6] found an excellent correlation between 107 pairs of RTs and ACTs ($r = .90$) in hospitalized adults. In 22 volunteers, ingestion of hot or cold liquids produced significant changes in oral temperature, but there was no significant change in ACTs. Green et al[12] found an excellent correlation between RTs and ACTs ($r = .90$) in 411 ambulatory adults. There was no significant difference between RTs and ACTs in their study.

Experimental work that supports using the tympanic membrane for temperature measurement comes from several sources. Using a thermistor placed in the esophagus and against the tympanic membrane, Wilson et al[7] found the latter to be equally sensitive during thermogenic stress in 44 burned children. Others have reported that tympanic thermistor measurement of body temperature was equally or more reliable during temperature changes in surgical patients than rectal or esophageal measures.[17,18] Infected tympanic membrane temperatures were not significantly different from uninfected contralateral ears in an experimental model of AOM in chinchillas.[12]

Using rectal temperature as the "gold standard" to assess ACTs for accuracy may have created falsely low sensitivity and specificity values for actual core body temperature. Rectal temperature has been shown to change slowly during rapid temperature changes, possibly due to vascular insulation from relatively poor blood flow to the normal rectum.[20] However, the rectum is the preferred measurement site in ambulatory children since it is unaffected by factors known to spuriously affect oral temperature, such as hyperventilation and recent ingestion of hot or cold liquids.[6] Axillary temperature measurement and liquid crystal forehead strips have been shown to be unreliable estimates of body temperature.[21-23] Esophageal and vascular thermistors are too invasive for routine temperature measurement in ambulatory patients.

This study has several limitations. Since nursing personnel were not blinded to ACT measurements, the potential for nursing bias was introduced. The standardized criteria for AOM may have been unreliable but are used by most pediatricians in evaluating children with AOM. This study did not seek to measure whether children older than 29 months of age were less cooperative. Other factors such as thermometer probe orientation or canal size may have accounted for the lesser accuracy in this age group.

In clinical practice, we find that ACT measurements are usually reliable. They are well accepted by children, parents, and nursing staff.[24] The probe and microprocessor has been shown to be easy to use, has excellent reproducibility, good acceptance by children and parents, is unaffected by factors influencing oral temperatures, and is a better indicator of RT than oral thermometers in adults.[6,12] Measurement of ACT appears to be a more appropriate temperature screening device than oral, axillary, or liquid crystal display thermometers. Occasionally there are patients who appear to have a 2°C- to 2.5°C-difference between RT and ACT measurements. Although some of these appear to be due to a low ambient temperature without adequate time for equilibration with a warmer environment, others are unexplained. We recommend further study in children before ACT systems replace RT systems when body temperature measurement is crucial.

We express our grateful appreciation to all the nurses, house staff, and faculty who participated in data collection and to Anne Milewski, RN, for staff orientation.

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Educational Interventions

Hugh D. Allen, MD, Columbus, Ohio
Fredric Burg, MD, Philadelphia, Pa
Harold Levine, MPA, Galveston, Tex
Barbara Starfield, MD, Baltimore, Md
Larrie W. Greenberg, MD, Washington, DC

Purpose.—This department is intended to share information concerning educational efforts in the broad field of pediatrics. We welcome studies on the following topics: undergraduate and graduate education in medicine and allied health occupations; continuing education of health professionals; education of patients and families; and health education for the general public, the community, and organizations that contribute to the promotion and improvement of the health of children.

Editorial Comment.—*All year long, pediatricians are inundated with school health questions and problems. These present a unique focus of attention, yet few of us were trained in school health issues. The authors of this report discuss such an aspect of their training program and its success.*—H.D.A.

School Health Training During Pediatric Residency

Virginia N. Niebuhr, PhD; David P. McCormick, MD; Stephen E. Barnett, MD

• Pediatricians are becoming increasingly concerned about reaching beyond the office or clinic to help solve problems of child and family health. The physician's ability to interact with school personnel and communities is one important approach to this outreach effort. School health training has been a required 6-month component of the pediatric residency curriculum at the University of Texas Medical Branch, Galveston, since 1979, with second-year residents providing weekly on-site consultations to public school districts and participating in a weekly school health seminar series. In this study, graduates from this program were surveyed to determine their evaluations of the training and extent of current school involvement and to use their evaluations for curriculum evaluation. Residents who participated in the school consultation from 1979 through 1988 were surveyed. Seventy-eight pediatricians responded, a 79% return rate. Ratings by the graduates reveal that both pediatric generalists and subspecialists highly value their training experiences. Ratings were not related to the specific site to which the resident consultant had been assigned. Of these pediatricians, 41% are currently consulting with school personnel. These findings are discussed as they relate to other reports of physician involvement in schools and provide clues to curriculum design for school health training in pediatric residency.

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Just as physicians in the 1800s and early 1900s went into schools to stem infectious epidemics,[1] pediatricians of today need to return to the school setting to address the "new morbidities" of children and adolescents.[2-4] Traditional office management of the child and family has had little impact on the present-day problems of drug use, adolescent pregnancy and sexually transmitted disease, poor nutrition and lack of exercise, serious behavioral and emotional disorders, and learning disabilities and attentional disorders. If change is to be effected, it is imperative that health care professionals address these problems through interaction with school personnel and community systems.

More than 10 years ago, in a monograph entitled "The Future of Pediatric Education,"[5] it was predicted that *all* pediatricians would soon be expected to manage child health in the context of the community. If pediatricians are to function effectively in schools and communities, they must be trained to do so. Pediatricians need to learn the structure of school systems, effective communication with schools, and consultative techniques. To this day, however, much of pediatric training continues to focus on hospital care, and to a lesser degree on outpatient clinical practice—all primarily within the context of the patient, and sometimes the family, rather than the school or community.

Prior to the mid-1970s there were no training programs or curricula to prepare pediatricians for potential new roles in school settings. In response to this void, several school health training programs were initiated during the 1970s,[6-10] including one at the University of Texas Medical Branch (UTMB) in Galveston. We describe herein the current design of this program and report on a follow-up of graduates who trained in this program during the past 10 years.

BACKGROUND AND PROGRAM DESCRIPTION

Since the mid 1970s, the UTMB school health training program has evolved from an elective for physicians,

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From the Department of Pediatrics, the University of Texas Medical Branch, Galveston.

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fellows, and residents[11-13] to a 6-month ambulatory core requirement for all second-year pediatric residents.[14-15] The major components of the program include weekly public school consultations, weekly school health/community pediatrics seminars, and clinical assessment and management of school-related problems in specialty teaching clinics.

Five Galveston County school districts currently contract with UTMB-Pediatrics for consultative services. Each second-year resident is assigned to spend one half day per week with a school district for 4 to 5 months in either a fall/winter or winter/spring rotation. School Health faculty provide back-up and act as mentors.

A major goal of the physician consultant program is for pediatricians in training to learn something of the environment in which their patients spend much of their time. Many pediatric residents do not have school-aged children and, indeed, have not been in a school since their own schooldays, yet the patient care they deliver often results from school referral, requires school involvement (eg, medication at school), or affects school performance (eg, behavioral effects of medical intervention and absence rates due to illness). Resident consultants are encouraged to visit a variety of regular and special education classes, to observe the most handicapped students served by the district, to teach a health-related topic to a class, and to interact with school nurses, administrators, and teachers.

A second major goal of the physician consultant program is for residents to learn about consultative processes. Residents are encouraged to consult rather than to provide direct patient care. Table 1 includes a list of potential activities of the consultants.

Resident consultants and their mentors meet to share consultative experiences and plan consultative activities. A weekly seminar series is designed to present a variety of school health and community pediatrics issues, using presenters from the UTMB faculty and staff and from the community. A sampling of topics that have been presented is included in Table 2.

Each resident is required to make a presentation during the rotation on a topic related to school health, a specific project developed through the consultation experience, or an individual case. In recent years, these presentations have included topics such as drugs, violence, pregnancy, discipline, and the impact of chronic handicaps, abuse, and prematurity.

Table 1.—Possible Contributions of the Resident Consultant in the Schools

- Individual case consultation
  - Consultation regarding students with special needs
    - Explaining medical conditions
    - Instructing teachers and staff about special equipment or procedures
    - Assisting teachers in explaining conditions to other students
  - Facilitation of referrals
  - Interpretation of medical records
  - Liaison between school personnel and other physicians
  - Assistance in determination of eligibility for special education services
  - Participation in planning conferences to develop strategies for students with special needs
- Program consultation
  - Provision of updated medical information to school nurses
  - Help with health screenings: planning, implementing, or evaluating
  - Involvement in health curriculum planning and implementation
  - In-service education of faculty and staff

Table 2.—Selected Topics Included in the School Health Seminar Series

- Anatomy and physiology of schools
- Consultation models and potential roles of a school health consultant
- Special education laws and services
- Attention-deficit–hyperactivity disorder
- Intellectual and educational assessment
- School health screening
- The school consultants role concerning chronic illness
- Community-oriented primary care: a model for needs assessment and program planning
- Health promotion/health education

School-related problems presented in general and specialty clinics at our health center are often complex and can easily overwhelm a resident during a busy day. Our child development clinic, behavioral pediatrics clinic, and chronic care clinic are specifically designed to handle complex school-related problems in a teaching climate (ie, opportunity to observe faculty, opportunity to be observed, and at least hour-long appointments). In these clinics, the residents judge what services they can provide vs when to refer, how to build and use referral networks, and how to include school personnel to facilitate assessment and management.

The purposes of the current project were to assess how valuable our school health training program has been to graduates, to document their current school-related activities, and to use their input for curriculum evaluation. Resident graduates were requested to rate the overall value of their consultation training experiences and the importance of specific curriculum components. They were also asked about their current school involvement.

A major question was whether there were discernible relationships between value ratings for school health training and subsequent school-related activity. We predicted that those who highly valued the training would be more likely to be currently involved in school consultation. In addition, comparisons were made between pediatric generalists and subspecialists to determine differences in their value ratings or in their current school-related practices.

METHODS

Between 1979, when the School Health Training Program became a required component of UTMB residency, and 1988, 100 residents participated in the program. Questionnaires were sent to 99 of these graduates (one is deceased), and a second mailing went to nonrespondents 5 months later.

On a five-point Likert scale with anchor phases, respondents indicated the overall value of their school consultation experiences. On a set of four-point Likert scales, respondents rated the importance of various curriculum components: school visits, consultation training, interaction with school nurses, and evaluation of school problems. On another set of four-point Likert scales, respondents indicated how well prepared they felt for interacting with school personnel, understanding the structure of schools, understanding the role of school nurses, being able to contribute to health education in schools, and assessing normal development.

Respondents indicated whether they were currently consulting with schools, either informally or through formal contract. Finally,

Table 3.—Frequencies of High and Low Value Ratings for Overall Experience and Curriculum Components*

	Value of Overall Training (n=73)		Making School Visits (n=76)		Learning to Evaluate School Problems (n=76)		Consultation Training (n=76)		Opportunities to Interact With School Staff (n=76)	
	High	Moderate	High	Low	High	Low	High	Low	High	Low
No. of respondents										
Generalists	37	18	49	6	53	2	46	9	35	20
Specialists	8	10	12	9	17	4	16	5	15	6
Test for comparison	$P=.084$		$P=.0003$		$P=.004$		$P=.45$		$P=.52$	

Some of the 78 respondents did not answer all questions.

y identified which of the following activi- s were part of their current professional rk: interaction with school administra- s, interaction with school nurses, assess- nt of normal development, and involve- nt in health education.

Data were analyzed using statistical soft- re (SAS, SAS Institute, Inc, Cary, NC). r nominal data, χ^2 analyses were used ien expected counts were greater than e, and Fisher's exact tests (two-tailed) re used when expected counts were less in five. Analyses of variances were made comparisons of interval data.

RESULTS

After both mailings, 78 question- ires were returned, a return rate of %. The mean (±SD) number of years it of residency was 4.6±2.8 (range, 1 9 years) and nearly equal numbers of omen (n=40, 51.3%) and men (n=38, .7%) responded. Pediatric generalists nstituted 73% of the respondents =57), and 27% were pediatric subspe- alists (n=21). Of the three pediatri- ans in public health, two identified iemselves as generalists and one as a ecialist in behavioral/developmental ediatrics.

The mean overall value rating was .55±0.82, where one means very valu- ble ("I am glad I had the experience") nd two means only moderately valu- ble ("It was okay, but I also could have one without it"). One respondent indi- ated no strong opinion, three indicated was not very valuable, and one indi- ated it was definitely not valuable. ince the frequencies for the "no opin- n" and low ratings were so small, only he high and moderate ratings were sed in subsequent analyses. Frequen- ies of high and moderate overall rat- ngs are presented in the first column of able 3. For their overall experiences, generalists gave more high-value than moderate-value ratings, and specialists gave more moderate-value than high-value ratings, although these differences are not statistically significant ($\chi^2=2.99$, $P=.084$).

Agencies with which these respondents had consulted during their residencies included seven independent school districts, one state school for handicapped students, and two community agencies (Head Start and Children's Protective Services). Most residents (n=54, 69%) had consulted at one of four school districts or Children's Protective Services. Analysis of variance reveals no significant differences in overall value ratings among these sites ($F=.46$, $df=4$, $P=.76$).

For analyses of the value ratings of the four curriculum components, the four-point Likert scales were collapsed into two categories: "high" (important) and "low" (unimportant). Frequencies of high and low ratings for generalists and specialists are presented in Table 3. High value ratings were given more often than low value ratings for all four curriculum components. Some differences emerged between ratings from generalists and specialists: generalists were more likely than specialists to highly value "making school visits" (Fisher's exact test, two-tailed, $P=.0003$) and "learning to evaluate school problems" (Fisher's exact test, two-tailed, $P=.004$). There were no differences between generalists' and specialists' value ratings of "consultation training during residency" ($\chi^2=.56$, $P=.45$) or "interactions with school nurses during residency" ($\chi^2=.41$, $P=.52$).

Preparedness ratings were collapsed into two categories (one and two indicated low preparedness, and three and four indicated high preparedness). Frequencies of high and low preparedness ratings for generalists and specialists are presented in Table 4. Comparison of preparedness ratings between generalists and specialists yielded significant differences only in the category of "able to contribute to health education." Generalists were more likely than specialists to believe themselves highly prepared (Fisher's exact test, two-tailed, $P=.007$). Ratings did not differ between groups for preparedness to interact with school personnel, understanding of the structure of schools, understanding of the role of the school nurse, or ability to assess normal development.

Table 5 shows the numbers of generalists and specialists who are currently consulting with schools, with and without formal contracts. School or community consultation is provided by 41% of the total sample (n=32), 47% of the generalists (n=27), and 24% of the specialists (n=5). The five specialists who consult represent the following areas: allergy (one), adolescent medicine (one), behavioral/developmental pediatrics (two), and neonatology (one), who indicated her consultation was in her role as a parent, not through her role as a neonatologist).

The likelihood of current consultation is not related to a high vs moderate value rating for the training experience ($\chi^2=1.50$, $P=.22$). That is, those pediatricians currently consulting were no more likely to have rated their experiences as highly valuable than moderately valuable.

Comparison of generalists and specialists on likelihood of current consultation yields no statistically significant difference ($\chi^2=3.52$, $P=.06$). Comparison of generalists and specialists on other specific school-related activities is

Table 4.—Frequencies of High and Low Preparedness Ratings (n = 70)*

	Contribution to Health Education		Interaction With School Personnel		Understanding of School Structure		Understanding Role of School Nurse		Assessment of Normal Development	
	High	Low	High	Low	High	Low	High	Low	High	Low
No. of respondents										
Generalists	46	8	46	8	43	11	50	4	51	3
Specialists	10	6	11	5	10	6	14	2	13	3
Test for comparison	$P = .007$		$P = .96$		$P = .95$		$P = .87$		$P = .98$	

*Some of the 78 respondents did not answer all questions.

Table 5.—Graduates Currently Involved in School Consultation

	Formal Consultation, With a Contract	Informal Consultation, Without Contract	Total No. Consulting
No. of respondents			
Generalists (n = 57)	14	18	27*
Specialists (n = 21)	0	5	5
Total (N = 78)	**14**	**23**	**32**

*Five generalists are simultaneously involved in formal and informal consultations with two or more agencies; therefore, this total is not a sum.

Table 6.—Comparisons of Generalists and Specialists on Current School-Related Activities

	Generalists, No. (%) (n = 55)*	Specialists, No. (%) (n = 21)	χ^2	P
Interaction with school administrators	24 (43.6)	4 (19.1)	3.95	.047
Interaction with school nurses	45 (81.8)	5 (23.8)	22.72	.0001
Assessment of development	51 (92.7)	12 (57.1)	13.57	.00007
Involvement in health education	26 (47.3)	6 (28.6)	2.18	Not significant

*Data incomplete.

summarized in Table 6. Neither group is very likely to interact with school administrators, although generalists are more likely to do so than specialists ($\chi^2 = 3.95$ $df = 1$, $P = .047$). Generalists are more likely than specialists to interact with school nurses, and more than 80% of the generalists do so ($\chi^2 = 22.72$, $df = 1$, $P < .0001$). Generalists are very likely to be involved in the assessment of development (93%), and they are more likely to do so than are specialists ($\chi^2 = 13.57$, $P < .0001$). Fewer than half of the physicians in both groups are involved in health education at more than the individual patient level, and generalists and specialists do not differ in the ikelihood of this activity ($\chi^2 = 2.18$, $df = 1$, $P = .14$).

Twenty-five percent (n = 14) of the generalists consult by contract, and none of the specialists do. Thirty-two percent (n = 18) of the generalists and 24% (n = 5) of the specialists consult without contract. Physicians with school-aged children are more likely to consult than those without school-aged children ($\chi^2 = 6.48$, $df = 1$, $P = .011$).

COMMENT

One major purpose of this study was to retrospectively evaluate school health training based on the perceptions of graduated residents. Overall, our graduates highly valued their school health training experience; very few perceived the experience as not valuable. Specifically, the graduates have indicated that they valued the opportunities to visit schools, to interact with school nurses, and to receive consultation training. On an open-ended optional question asking for comments about the school health training program, 69% (n = 54) of the respondents answered, and the comments were generally positive or constructive. Several respondents encouraged continuation of the program. Many acknowledged the importance of learning to deal with the school-related issues of their patients and reported frustration at not having learned even more.

The 79% return rate is high, but there remains the question of how nonrespondents might have evaluated the training experience. Perhaps those who valued the experience the least were also the least likely to respond to a survey, thus skewing the results in a more positive direction. Ratings could also be positively skewed by factors such as wording of the Likert scale anchors or respondents' eagerness to look good or reluctance to be critical.

The program faculty expected variations in ratings between different consultation sites. However, value ratings did not differ between sites, indicating that the training experience can be valuable despite individual site differences. In the open-ended questions, respondents shared some of the frustrations of their school health training experiences, yet highly valued those experiences overall. We contend that even frustrating experiences can be valuable for learning about the consultative process.

A second major purpose of our survey was to determine the respondents' current school involvement. In our sample, 41% indicated that they currently consult with school personnel. In Chilton's[16] sample of pediatricians in the South-est 10 years ago, 65.6% provided some hool health services. Ten years later, reports based on a national sample of ediatricians, Nader[17] and Black et al[18] oted that 77% are involved in school-elated activities.

The apparently higher rates of school volvement in Chilton's and Nader's amples compared to ours may reflect hese investigators' broader definitions f school health involvement. We queed specifically for consultation activies. The differences in rates may also eflect regional differences in school ealth activities. Finally, the highest volvement rate, reported by Nader nd Black et al, may be inflated by a ower return rate (46%). Respondents ay have been more likely than nonrepondents to be involved in schools.

One of our initial questions was hether there is a relationship between erceived value of training and subseuent school involvement. Nearly all of he respondents, either currently conulting or not, gave high or moderately igh ratings for the training. Those curently consulting gave ratings that howed no statistical differences beween the high and moderately high catgories. In addition, although nearly all he graduates valued the training, not ll are currently involved with schools. That is, valuing the training does not ecessarily result in current involvenent. This suggests that the relationhip between perceived value of trainng and subsequent school involvement s not direct.

Chilton discusses the relationship beween presence or absence of school ealth training and subsequent school nvolvement. He suggests that training n school health arouses a pediatrician's interest in interacting with school personnel. Of his sample, 22% had received school health training, but 65.5% were involved in schools. In the studies by Black et al and Nader, 18% of the physicians had received school health training, but 77% were involved in schools. Although all of our subjects had received school health training, only 41% reported current involvement. Taken together, these three sets of data suggest little direct relationship between presence or absence of school health training and current school involvement. We conclude that neither the perceived value of the training nor school health training per se results in pediatricians interacting with school personnel. The findings of Chilton and Black et al indicate that many pediatricians will become involved with schools even without specific training in school health. Perhaps this is because of increasing community needs or demands for pediatricians' involvement to help solve the complex problems of children and adolescents.

We also conclude that the important question is not whether school health training creates school health involvement, but how we can best prepare pediatricians for this involvement. This question leads directly to examination of our school health curriculum. We have identified three elements of our curriculum that need further attention: training in administrative issues, health education in schools, and school health as it relates to both general and subspecialty pediatric practices.

The few formal contracts obtained by our repondents (25% of generalists and no specialists) and the infrequency of their current interaction with school administrators (43.6% of generalists and 19.1% of specialists) could reflect lack of skill or confidence in contract negotiation and dealing with school administrators. These findings suggest that increasing the emphasis on these aspects of school consultation in our curriculum would be beneficial.

Disappointingly few physicians in our sample indicated involvement in health education beyond the individual patient level, despite their perception that they were well prepared for such involvement. Generalists believed themselves better prepared than specialists, but were no more likely than specialists to be involved in this activity. We must examine how effectively we teach residents about their potential role in school and community health education, raise the valence for pediatricians' involvement in health promotion, and cultivate a realization that schools can be ideal environments for promoting healthy habits and life-styles for children.

Nearly one fourth of the specialists and nearly half of the generalists are currently consulting with school personnel, although generalists and specialists did not differ in their overall value ratings of school health and consultation training. These findings emphasize our need to integrate school health issues into both primary care and subspecialty care and to continue to provide school health training for all pediatric residents, even those heading for subspecialties.

One difference that did emerge between generalists and subspecialists was that subspecialists were much less likely than generalists to interact with school nurses in their current work. The infrequency of specialists' current contact with school nurses is disappointing, since presumably many specialists could use the school nurse to help implement complex treatment plans, communicate with families, and monitor patients' daily functioning. We conclude that a stronger emphasis is needed on the potential interactions of pediatric subspecialists school staffs for the care of students with special health problems. This might be accomplished through greater involvement in the school health training program by the subspecialty faculty.

To provide more effective training in school health, we need to identify factors that promote or inhibit pediatricians' participation in school health. It was not surprising that among our respondents the likelihood of school involvement increased if the pediatrician had children in school. Unfortunately, we did not obtain data on when in their pediatric careers our graduates began consulting with schools. This leaves unanswered the question of whether pediatricians use school interactions as practice-builders or branch into school consultation after their practices are well established and they are searching for diversity.

Investigations of incentives, reinforcements, and remunerations for physician involvement with schools might help reveal how pediatricians can become more involved with schools. Investigations of how physician involvement in schools is affected by attitudes of school health personnel toward physician interaction may also be useful, as might investigations of whether requests for medical consultation are related to the absence or presence of school nurses and health educators in school systems.

For continued improvement of school health training for physicians, other questions need investigation. What do practicing pediatricians identify as important knowledge and skills for effective work with schools? How can continuing medical education at the postresidency level be used to provide training in school consultation? We intend to use our graduates' evaluations to further develop and refine our training program in hopes that we can better prepare pediatricians to meet the challenges of pediatrics through interactions with school personnel.

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JAMA

HIV Infection, Pregnant Women, and Newborns
Working Group on HIV Testing of Pregnant Women and Newborns (*JAMA.* 1990;264:2416)

A Formal Audit of Continuing Medical Education Activity for License Renewal
J. K. Stross; T. J. DeKornfeld (*JAMA.* 1990;264:2421)

Continuing Medical Education at a Crossroads
Dennis K. Wentz (*JAMA.* 1990;264:2425)

The Federal Regulation of Prescription Drug Advertising and Promotion
D. A. Kessler, W. L. Pines (*JAMA.* 1990;264:2409)

Nevus Flammeus

Discordance in Monozygotic Twins

Raanan Shamir, MD; Gertrude Kohn, MD; Aryeh Metzker, MD

• Nevus flammeus has been described as an inherited vascular anomaly. We report two cases of nevus flammeus, each appearing in one of two monozygotic twins. This finding supports the idea that nevus flammeus results from embryologic mishap rather than genetic transmission.

***(AJDC.* 1991;145:85-86)**

Nevus flammeus (NF), or port-wine stain, is a pink to purple vascular nevus, located anywhere on the skin, but occurring most often on the face. It persists throughout life and has an incidence of 0.5%.[1] The psychological burden to a child with such a blemish is obvious. Apprehensive parents of a child with NF often voice their reluctance to have more children because of the fear that NF, as an inheritable phenomenon, might recur. Publications that describe familial NF and suggest an autosomal dominant inheritance with irregular penetrance give credence to this fear.[2-5]

Our study of two pairs of monozygotic twins provides evidence that NF is not transmitted genetically.

PATIENT REPORTS

PATIENT 1.—A 3-year-old girl, an identical twin, was seen in the Pediatric Dermatology Clinic of Beilinson Medical Center, Petah Tiqva, Israel, for a light purple discoloration on her left cheek. This patch appeared as a typical NF and had not changed since birth, except that it became slightly more pronounced in color. The girl was otherwise well, and results of her physical examination were normal.

Her twin sister had no such discoloration and was well in every respect. The two girls resembled each other remarkably (Fig 1). Their dermatoglyphic patterns were almost identical. Their HLA alleles (A2, B38, B39, B42, and W7, with identical response to 120 antisera) and blood groups and subgroups (0+, E+, C+, M+, and N−) were identical.

PATIENT 2.—A 13-year-old boy, an identical twin, was seen in Beilinson Medical Center's Pediatric Dermatology Clinic for a large NF covering half of the nape (Fig 2). Results of his physical examination were normal. His twin brother did not have an NF, but the two brothers otherwise resembled each other remarkably (Fig 3). The two brothers were monochorionic and monoamniotic, and had identical blood groups and subgroups (AB+, C+, M+, and N+) and identical HLA alleles (A1, A24, B57, B35, W4, DR5, DR6, DQw1, DQw3, and DRw52). Their parents' HLA alleles were not identical.

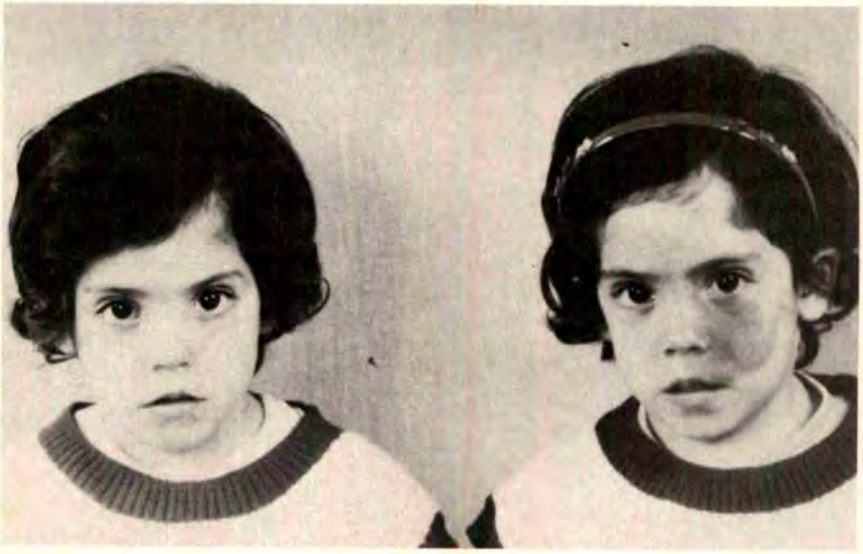
COMMENT

To the best of our knowledge, these cases are the first reported occurrences of NF appearing in only one of two identical twins.

The occurrence of an NF in only one of two monozygotic twins indicates that such a nevus is not part of the genetic code. All twins in our report strikingly resembled their twins and had the same HLA alleles and blood groups as their twins. All these factors render remote the possibility of their not being monozygotic sets of twins.

Nevus flammeus is a localized ectasia of capillaries in the upper dermis caused

Fig 1.—Identical twin sisters (case 1). One has a nevus flammeus on her left cheek.



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From the Units of Pediatric Dermatology (Drs Shamir and Metzker) and Medical Genetics (Dr Kohn), Beilinson Medical Center, Petah Tiqva, Israel, and Sackler School of Medicine, Tel Aviv (Israel) University.

Reprint requests to Pediatric Dermatology Unit, Beilinson Medical Center, Petah Tiqva 49 100, Israel (Dr Metzker).

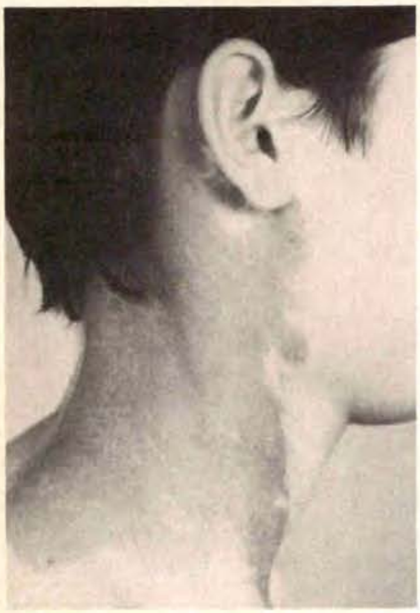

Fig 2.—Nevus flammeus on the neck and nape (case 2).

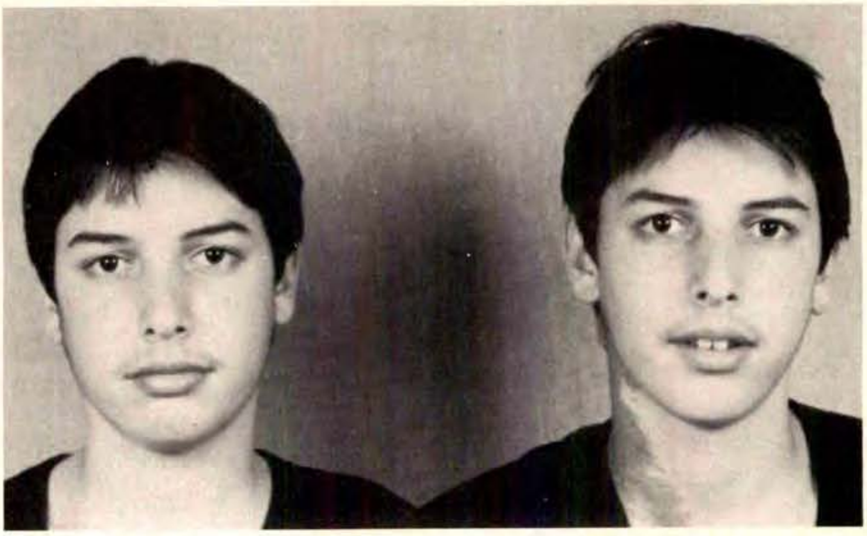

Fig 3.—Identical twin brothers (case 2). One has a nevus flammeus on his nape.

by a circumscribed nervous dysfunction of the vascular plexus or loss of sympathetic neurons.[6] The relatively high incidence of NF makes reappearance of NF likely in the same family. Curiously enough, two reports[2,4] refer to multiple NFs, which are uncommon. Nevertheless, the appearance of such a nevus in siblings and their parents is not sufficient to suggest a dominant inheritance, as claimed in those two reports.

Two other authors[3,5] describe familial NF of the forehead. A clear distinction between true NF, which persists throughout life, and NF simplex, which is mostly transient, is called for. Nevus flammeus simplex combines erythema nuchae, alias "stork bite," and the salmon patch of face, alias "angel kiss." Nearly 50% of newborns have NF simplex. The salmon patch clears, in most cases, during the first year, but shades of it might persist into adulthood. The stork bite is slower in disappearing. It seems likely that Selmanowitz[3] and Merlob and Reisner[5] were describing cases of persistent salmon patch.

It might be possible that monozygotic twins, discordant for a cryptogenic trait, have a genetic cause for their disorder; this could be explained by heterogenic monozygocity.[7] For all practical purposes, the occurrence of NF in only one of two identical twins attests either to absence of a genetic factor in this disorder or to a new mutation not present in the parental DNA. Both suggest embryologic mishap as a cause of NF. Further, despite extensive literature on Sturge-Weber syndrome, which also involves NF, no evidence for genetic tendency can be found.

Today, the psychological distress caused by NF can sometimes be alleviated by lightening the stain with tunable pulsed-dye laser therapy.[8] Nevertheless, anxious parents with NF or parents of children with NF may be reassured that another case of NF is probably no more likely to occur in their families than in the general population. If inherited at all, NF may be a rare phenomenon based on multifactorial inheritance.

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Neural Arch Stenosis and Spinal Cord Injury in Thanatophoric Dysplasia

Ona Marie Faye-Petersen, MD, A. S. Knisely, MD

• Bony abnormalities caused by thanatophoric dysplasia affect the base of the skull and the vertebrae as well as the ribs and appendicular long bones. We present our findings in a full-term infant with thanatophoric dysplasia in whom the posterior fossa, the rostral vertebral column, and the neuraxis at and adjoining the craniovertebral junction were studied by dissection, roentgenography, and histologic examination. In this infant, malformations of the vertebral laminae, most prominent in the basiocciput and atlas vertebra, led to compression of the rostral cervical spinal cord, causing gliosis and focal necrosis. Stenosis of the foramen magnum and spinal canal may contribute to the ventilatory insufficiency that often causes death in patients with thanatophoric dysplasia. We suggest that the causes of death in patients with thanatophoric dysplasia and other severe forms of osteochondrodysplasia should be sought in neuraxial injury rather than attributed solely to pulmonary hypoplasia.

(*AJDC.* 1991;145:87-89)

In thanatophoric dysplasia (TD), the limbs are short, the thorax is small, and the clivus and posterior fossa are hypoplastic.[1-3] These deformities result from disordered endochondral ossification.[4] Reduced thoracic dimensions in TD are frequently associated with moderate pulmonary hypoplasia,[5] to which, at least in part, death is generally ascribed.[1] The vertebral laminae, components of the neural arch, are endochondrally formed, and stenosis of the foramen magnum has long been recognized in TD.[2,3] We examined the basiocciput, vertebrae, and spinal cord of a full-term infant with TD. We found malformations, deformation, and potentially significant neuraxial injury, principally at the level of the atlas vertebra, that may have contributed to ventilatory failure.

PATIENT REPORT

Clinical History

A 19-year-old woman presented for initial evaluation in the 42nd week of gestation by dates. She described the pregnancy, her fourth, as uncomplicated. The family history was unremarkable. Sonography identified short-limbed osteochondrodysplasia and breech presentation. After a short period of spontaneous labor, a male infant was born by cesarean section. Thick meconium was in the amniotic fluid. Craniomegaly, short limbs, and poor ventilatory effort were noted at birth. Endotracheal intubation was performed for pulmonary toilet; ventilatory support was continued pending evaluation. Skeletal roentgenograms showed short, curved femora, squared iliac bones, platyspondylisis, and subperiosteal juxtaphyseal spurring. These findings were consistent with TD. After consultations with the parents, ventilatory support was discontinued on the third postnatal day, and the infant died within 5 minutes. Skin fibroblasts from the infant were cultured and banked (National Institute of General Medical Sciences Human Genetic Mutant Cell Repository GM10749, Coriell Institute for Medical Research, Camden, NJ).

Necropsy Techniques

After standard necropsy evisceration, the posterior fossa and rostral spinal column were excised en bloc, including the in situ neuraxis distal to the obex.[6] The posterior fossa and vertebrae C-1 through T-1, with the encased length of spinal cord in situ, were fixed in 10% phosphate-buffered formaldehyde solution. Individual vertebrae were separated at the levels of the intervertebral disks using sharp dissection. Roentgenograms of the posterior fossa with basiocciput and of vertebrae C-1 through T-1 were exposed with the specimens in contact with the cassette to avoid magnification. The vertebrae and fossa were decalcified in 8% sulfosalicylic acid, hemisected transversely, and embedded in paraffin. Whole-mount sections were stained with hematoxylin-eosin, Masson's trichrome, periodic acid–Schiff, Luxol fast blue–cresyl violet, Bodian, and immunoperoxidase. A portion of the spinal cord at the level of the atlas vertebra was postfixed and routinely processed for transmission electron microscopy.

Necropsy Results

Findings included megalencephaly (brain weight, 577 g; normal,[7] 362 ± 55 g) with temporal-lobe gyral abnormalities characteristic of TD,[5] posterior-fossa hypoplasia, and rostral herniation of the cerebellum through the tentorial leaflets. The lungs were hypoplastic on gross examination and weighed 29 g together (normal lung weight,[7] 56 ± 15 g). Aspirated meconium without pneumonitis was seen on microscopic examination. The cartilaginous framework of the larynx, trachea, and bronchi was unremarkable grossly; on microscopic examination, however, architectural immaturity and chondrocyte disarray were apparent. Sections of iliac crest and costal physes showed the effects of TD.[4] Stenosis of the midportion of the ductus arteriosus, without typical postnatal proliferative changes, and right ventricular hypertrophy also were noted.

Contact roentgenograms and tissue sections showed malformations of the vertebral laminae, which were shortened and bowed ventrally and medially, with periosteal bony spurring and disordered ossification at the physes. Malformation was most pronounced in the basiocciput, which showed stenosis and ventral displacement of the foramen magnum (Fig 1), and in the C-1 vertebra. The

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From the Department of Pathology, Primary Children's Medical Center (Dr Faye-Petersen) and the Departments of Hematology and Pathology, University of Utah Medical Center (Dr Knisely), Salt Lake City.

Reprint requests to Department of Pathology, Children's Hospital of Pittsburgh, One Children's Pl, Pittsburgh, PA 15213-3417 (Dr Knisely).

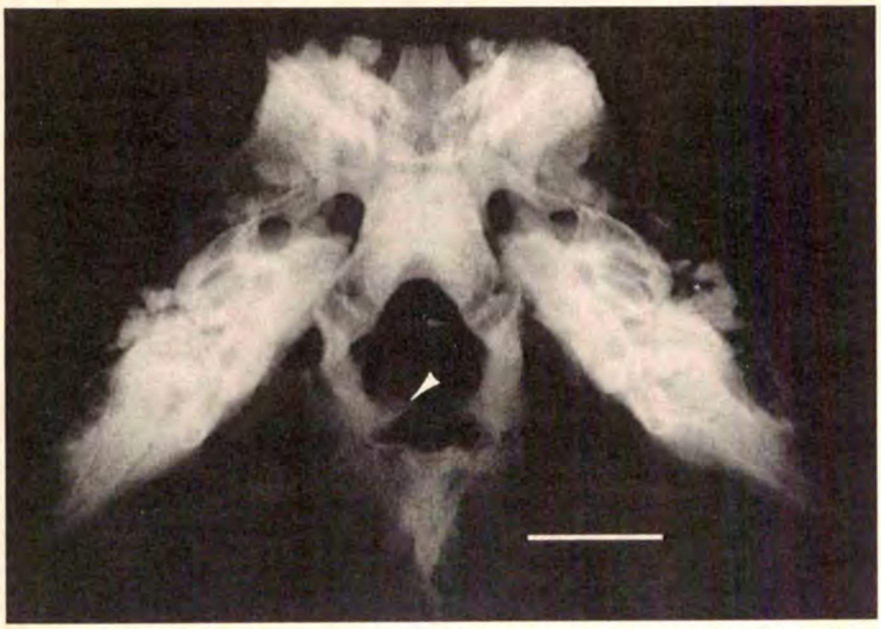

Fig 1.—Contact roentgenogram of the posterior fossa of the patient. The contours of the foramen magnum of an infant without osteochondrodysplasia are smooth[12]; here, the occipital laminae are shortened and incurved, and the lumen of the foramen magnum is irregularly narrowed by bony protuberances that represent the physes of the occipital laminae.[2,3] Note the juxtaphyseal bone spurs, one of which is indicated by an arrowhead, in the occipital laminae and body. Similar spurring is well recognized at proximal femoral physes in thanatophoric dysplasia (original magnification × 2; bar equals 1 cm).[4]

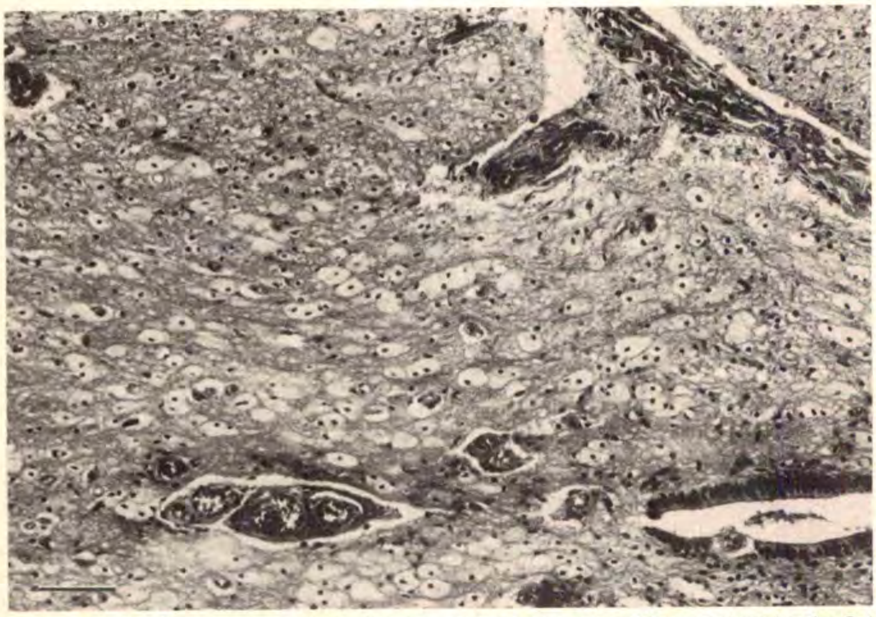

Fig 2.—Swollen immature astroglial cells in the central gray matter of the spinal cord at the C-1 level. The central canal, which is flattened anteroposteriorly, is at the lower right, and the tortuous anterior spinal vessels are at the upper right (Luxol fast blue-cresyl violet, original magnification × 180; bar equals 80 μm).

spinal cord was deformed at all levels, fitting snugly within the triangular lumen of the spinal canal, and was rotated 45° to the right at the L-1 level.

Injury, as opposed to deformation, of the spinal cord was present from the foramen magnum through the C-3 level. It was most conspicuous at the C-1 level, where swollen immature astroglial cells[8] (Fig 2) were identified ventral to the central canal and in the uncrossed corticospinal tracts. Vascular congestion with endothelial reactive changes was marked. Axonal swellings and gliosis with mature reactive astrocytes also were present (Fig 3), but were more numerous at the C-2 and C-3 levels. Gliosis with reactive astrocytes and small clusters of lipid-laden macrophages (gitter cells) were seen at the level of the foramen magnum. Gliosis was not observed caudal to the C-4 level or in the medulla immediately above the level of the foramen magnum. Reactive astrocytes stained well for glial fibrillary acid protein, while the cytoplasm of enlarged immature astroglial cells stained only faintly. Neuronal loss, degenerative changes, and pyknosis were not apparent. Transmission electron micrographs showed only advanced autolytic change that precluded meaningful ultrastructural analysis.

COMMENT

This infant with TD had abnormally short and incurved vertebral and modified vertebral (basioccipital) laminae, with consequent stenosis of the spinal canal and foramen magnum. The entire spinal canal was stenotic, but was relatively less narrowed caudally to C-1. Our dissection did not identify a cause for rotation of the lumbar spinal cord within the spinal canal.

The neural arch fit closely around the distal medulla and the rostral cervical spinal cord, which showed marked compressive deformity and injury manifested as necrosis, gliosis, and unusual cytoplasmic changes in immature astroglial cells. The lesions affected predominantly the ventral cord and were essentially limited to the region immediately caudal to the craniovertebral junction; we propose that this suggests compression of the cord against the dens of the axis vertebra (body of the atlas vertebra) during flexion of the head and neck. The injury seen could have led to impaired diaphragmatic function and, hence, to impaired ventilation. Gliosis, vacuolation, and macrophages in the cervical spinal cord, as documented here, have been observed in at least one other newborn with TD,[5] and are consistent with antenatal onset of injury. These findings may be correlated not only with ventilatory failure but also with polyhydramnios[9] (possibly due to impaired swallowing) and decreased fetal motion,[10] which are both commonly

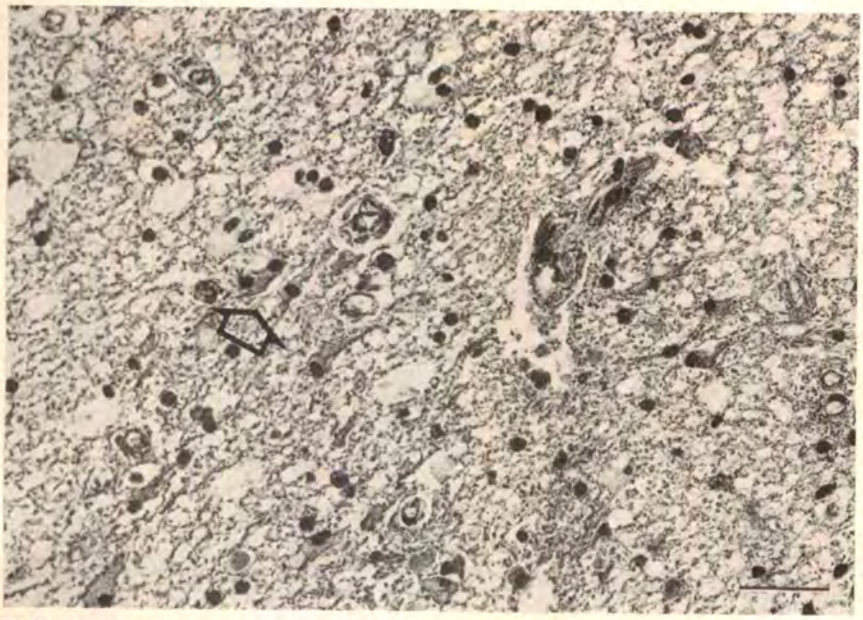

Fig 3.—Mature reactive astrocytes (arrow) and rare swollen immature astroglial cells in uncrossed corticospinal tract at the C-2 level (hematoxylin-eosin, original magnification × 575; bar equals 30 μm).

associated with TD.

Neural arch malformation with neuraxial deformation is recognized in other forms of osteochondrodysplasia,[11-14] in which it is associated with ventilatory dysfunction that can be surgically relieved.[14] Release of the neuraxis by suboccipital craniectomy has allowed two individuals with TD and ventilatory dysfunction to survive for several years; one of them had evidence of brainstem compression on measurement of auditory evoked potentials. These children remained ventilator dependent.[15] Our findings indicate that compressive deformity at C-1 and foramen magnum levels may be a significant complication of TD. If potentially life-sparing surgery is performed to combat the effects of TD, it may be necessary to unroof the neuraxis in the rostral spinal canal as well as at the craniovertebral junction. Evaluations of thoracic wall mechanics, pulmonary function, and brain-stem and phrenic evoked potentials (to assess the extent to which abnormalities in thoracic and diaphragmatic conformation, anatomy of the cartilaginous airways, and neuraxial injury may contribute to ventilatory insufficiency) should perhaps precede such procedures. To our knowledge, these studies have yet to be performed in individuals with TD.

Thoracic malformations, abnormalities in lung mesenchyme, and neuraxial injury all may be present in osteochondrodysplasia. These lesions may produce both pulmonary hypoplasia and ventilatory insufficiency of multifactorial cause.[16-18] Assessment of skeletal and neuraxial abnormalities at the craniovertebral junction and in the rostral cervical spine and spinal cord, as performed in this patient, facilitates study of the contributions of thoracic, pulmonary, and neural-arch malformations to the ventilatory insufficiency seen in many forms of osteochondrodysplasia.

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Marfanoid Children

Etiologic Heterogeneity and Cardiac Findings

Shawky Tayel, MD; Thaddeus W. Kurczynski, MD, PhD; Marc Levine, MD; Ernest Brookfield, MD;
Robert Ehrlich, MD; James R. Hennessy, MD; Martin M. DeBeukelaer, MD

• The clinical, cardiac, and echocardiographic test results of 20 children with marfanoid features are reviewed. Fifteen were diagnosed as having Marfan syndrome, two had "possible" Marfan syndrome, and three had other diagnoses. On first evaluation, eight patients with Marfan syndrome (53%) had mitral regurgitation and none had aortic regurgitation. Echocardiography showed aortic root enlargement in 12 (80%) of 15 patients and mitral valve prolapse in 12 (80%) of 15. None had a normal echocardiogram. At follow-up examination, one patient had developed aortic root enlargement, and one patient, mitral valve prolapse. Thus, although aortic root enlargement is usually present in early childhood in patients with Marfan syndrome, it is not considered specific because in this study it also occurred in one child with Alport's syndrome and in one with marfanoid features. Four patients with aortic root enlargement were treated with propranolol and their echocardiograms showed no further increase in the aortic root diameter for several years. We recommend echocardiography in the diagnosis and routine management of children in whom Marfan syndrome is suspected.

(*AJDC.* 1991;145:90-93)

A marfanoid appearance consisting of a variable combination of a tall slender body build, long extremities and digits, pectus deformity, scoliosis, and myopia is relatively common. When such children seek medical attention, the question of Marfan syndrome is often raised. This specific autosomal-dominantly inherited disorder of connective tissue has important cardiovascular manifestations but is only one of the causes of a marfanoid appearance.[1-4] No specific diagnostic test is yet available, and since various marfanoid features are age dependent, the diagnosis of Marfan syndrome may be more difficult in young children. Clinical criteria, however, have been established.[2] In this study, we present a retrospective analysis of the clinical and echocardiographic findings of 20 marfanoid children, 15 of whom met the criteria for the diagnosis of Marfan syndrome and were followed up for at least 6 months.

PATIENTS AND METHODS

We reviewed the medical records of all children under 17 years of age evaluated between 1980 and 1987 at the Medical College of Ohio Hospitals, Toledo, with a suspected diagnosis of Marfan syndrome. The diagnosis of Marfan syndrome was based on the presence of abnormalities in three or more of the following four categories: skeletal, ocular, cardiovascular, and family history.[2]

Skeletal and Connective Tissue

- Tall stature
- Dolichostenomelia
- Arachnodactyly
- High arched palate
- Joint laxity
- Anterior chest deformity (pectus excavatum or carinatum or a combination)
- Scoliosis
- Pes planus
- Inguinal hernia

Ocular

- Myopia
- Lens subluxation (ectopia lentis)
- Flat cornea (less than 42 by keratometer)
- Retinal detachment

Cardiovascular

- Aortic root dilatation
- Mitral valve prolapse
- Mitral regurgitation
- Aortic regurgitation
- Aortic dissection

Positive Family History

Children with skeletal findings and abnormalities in fewer than three categories were considered marfanoid. All subjects underwent complete clinical examination and detailed M-mode and two-dimensional echocardiographic studies. Aortic regurgitation (AR) and mitral regurgitation (MR) were detected clinically, since complete Doppler evaluation was not available for many of the patients. Nine patients were followed up for an average of 34 months (range, 6 to 60 months). Four patients were treated with propranolol to prevent aortic root enlargement (ARE) and dissection.[4,5]

Echocardiography was performed using standard techniques.[6] Left ventricular diastolic dimension, aortic root dimension, and left atrial dimension were measured as described by Sahn et al.[6] Mitral valve prolapse (MVP) was defined as deflection of a mitral leaflet posterior to the "C" point by at least 2 mm throughout systole or beginning of diastole. Each measurement was plotted as a linear function of body surface area, with normal values defined as those falling within 95% of predicted values for normal children as described by Henry et al.[7]

RESULTS

The clinical features of the 20 patients are summarized in the Table. The most frequent skeletal abnormality was a pectus deformity in 16 patients (80%).

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From the Department of Pediatrics, Medical College of Ohio, Toledo.

Presented at the First International Symposium on the Marfan Syndrome, Baltimore, Md, July 9, 1988.

Reprint requests to Department of Pediatrics, Medical College of Ohio, CS 10008, Toledo, OH 43699 (Dr Kurczynski).

Clinical Findings of 20 Marfanoid Children*

Patient No./Sex	Age at Last Evaluation, y	Age at Diagnosis, y	Skeletal Features								Ocular Features		Cardiac Features						Family History	Diagnosis
			Ara	Dol	Sco	PD	PP	JL	HAP	IH	EL	Myo	MR	MVP	AR	ARE	LVE	LAE		
1/M	15	6	+	+	+	−	−	−	+	−	+	+	+	+	−	+	−	−	−	MS
2/M	10	7	+	+	+	+	−	−	+	−	+	+	+	+	−	+	−	−	Mo	MS
3/F	15	8	−	+	+	+	−	+	+	−	−	−	−	−	−	+	−	−	Fa	MS
4/F	13	7	+	−	−	+	−	−	+	+	+	+	+	+	−	+	+	−	−	MS
5/F	11	7	−	−	−	+	−	−	−	−	−	+	−	+	−	−	−	−	Fa	MS
6/F	15	13	−	+	−	−	−	−	+	−	−	+	+	−	−	−	+	−	−	MS
7/M	9	2	−	+	+	+	−	−	+	+	−	+	+	+	−	+	+	+	Fa	MS
8/M	9	4	−	−	−	+	+	+	−	−	−	+	+	+	−	+	−	−	Mo	MS
9/F	17	12	+	−	+	+	−	−	+	−	−	+	−	+	−	+	−	−	Mo	MS
10/M	14	10	+	−	+	+	−	+	−	−	+	+	+	+	−	+	−	+	Mo	MS
11/M	10	8	+	−	−	+	−	−	−	−	+	+	+	+	−	+	+	+	−	MS
12/M	16	15	+	−	−	−	+	−	−	−	−	+	−	+	+	+	+	+	−	MS
13/F†	15	14	−	+	+	+	+	+	−	−	−	−	−	+	−	+	−	−	Fa	MS
14/F†	9	9	−	+	+	+	+	+	−	−	−	−	−	+	−	+	−	−	Fa	MS
15/M†	12	12	−	+	+	+	+	+	−	−	−	−	−	+	−	+	+	−	Fa	MS
16/F	14	7	+	−	+	+	−	+	+	−	−	−	+	+	+	+	−	−	−	MA
17/M	14	11	−	−	+	−	−	−	+	−	−	−	+	+	−	+	+	+	NA	MA
18/F	12	11	−	+	+	+	−	−	−	−	−	+	−	+	−	−	−	−	−	MA with neurofibromatosis
19/M	15	10	−	+	+	+	−	−	−	−	−	−	−	−	+	+	+	−	−	MA with Alport's syndrome
20/M‡	17	13	−	+	+	+	+	+	+	+	−	+	+	+	−	+	+	−	−	Marfanoid syndrome with craniosynostosis[10]

*Ara indicates arachnodactyly; Dol, dolichostenomelia; Sco, scoliosis; PD, pectus deformity; PP, pes planus; JL, joint laxity; HAP, high arched palate; IH, inguinal hernia; EL, ectopic lentis; Myo, myopia; MR, mitral regurgitation; MVP, mitral valve prolapse; AR, aortic regurgitation; ARE, aortic root enlarged; LVE, left ventricle enlarged; LAE, left atrium enlarged; Mo, mother; Fa, father; MS, Marfan syndrome; MA, marfanoid appearance; NA, not available; plus signs, presence of listed features; and minus signs, absence of listed features.

†These patients are siblings.

‡Patient died suddenly of aortic dissection.

The least frequent findings were inguinal hernia and pes planus, present in three patients (15%). Myopia was seen in 13 patients (65%) while only five patients (25%) had ectopia lentis. Ten patients had a parent with Marfan syndrome, in nine patients the disease was sporadic, and one patient was adopted, with unknown family history.

Fifteen of the children were diagnosed as having Marfan syndrome. Two children, patients 9 and 17, were considered possible patients with Marfan syndrome because they met two of the four criteria, including the presence of ARE and MVP.

Patients 18, 19, and 20 were marfanoid with other diagnoses. Patient 18 was a black girl who was referred for genetic evaluation at age 12 years because of multiple cafe au lait spots and marfanoid features. There was also a history of learning disability. Her examination showed significant findings: a slender appearance, dolichostenomelia, myopia, an alternating exotropia, multiple cafe au lait spots, axillary freckling, a probable neurofibroma of the left heel, pectus excavatum, scoliosis, a systolic click, an enlarged thyroid, and mild incoordination. Echocardiography showed MVP but no ARE. She was diagnosed as having hyperthyroidism and treated with propylthiouracil. The family history was negative for cafe au lait spots, neurofibromatosis, or marfanoid features.

Patient 19 was a boy with Alport's syndrome. He had progressive renal insufficiency and sensory neural hearing loss. At age 15 years, he was 187 cm tall and weighed 67.3 kg. Skeletal abnormalities included a tall, slender appearance, dolichostenomelia, maxillary hypoplasia, a prominent mandible, pectus carinatum, and scoliosis. There was no arachnodactyly or ectopia lentis. Echocardiography and cardiac catheterization performed to rule out a possible aortic root dissection demonstrated ARE (aortic root diameter, 4.4 cm; normal, 2.1 to 2.8 cm), and he was treated with propranolol. He received a renal transplant at 16 years of age. At this writing, he was 18 years old, was mildly hypertensive, and had a well-functioning kidney graft. There has been no further ARE. The family history was significant in that his mother and three brothers also had Alport's syndrome. His two other brothers required kidney transplants at ages 13 and 15 years, respectively. One of his brothers had been receiving long-term hemodialysis when he died at age 13 years of a dissecting aortic aneurysm. Although this patient never had an echocardiogram done, his autopsy revealed a normal aortic root diameter. One brother was nearsighted and had mild pectus excavatum, and the other had scoliosis and mild pectus excavatum. None of the family members had a marfanoid appearance, and their echocardiographic studies showed no cardiac abnormalities.

Patient 20 was a boy who died at 17 years of age of a dissecting aortic aneurysm. He had features typical of Marfan syndrome, such as dolichostenomelia, scoliosis, pectus carinatum, myopia, and recurrent inguinal hernia. There were, however, atypical anomalies such as craniosynostosis, ptosis of the eyelids, hypospadias, and spondylolisthesis. Ectopia lentis was absent. He was the only one in the family affected and had four normal siblings. He was previously described as a patient with a new marfanoid syndrome.[8]

The cardiovascular features of the 20 patients are summarized in the Table. On initial examination, five patients had a midsystolic click, 11 had a pansystolic apical murmur of MR, and one had a murmur of AR. The most frequent abnormalities at the initial echocardiographic examination were ARE, present in 15 patients (75%), and MVP, present in 16 patients (80%). Increased left ventricular diastolic dimension was detected initially in nine patients (45%); six of these patients had MR, one had AR, and two had neither MR nor AR.

During the period of the study, four additional patients developed a systolic click and two developed combined MR and AR. Eight patients had progression of mitral valve dysfunction defined by the appearance of a new systolic click, an increase in the murmur of MR by at least two grades, the appearance of left ventricular enlargement in the absence of AR.

Repeated echocardiograms were available for nine patients who were followed up for an average of 34 months (range, 6 to 60 months). Seven of these patients were initially found to have ARE at a mean age of 11.8 years (range, 4 to 15 years), and the other two developed it during the period of study (at 8 and 13 years of age). No patient developed ARE greater than 4.6 cm over the period of the study. Six of the nine patients had MVP initially at a mean age of 8.5 years (range, 4 to 14 years), two more patients developed it during the study period (at 17 and 16 years of age), and one patient did not develop it.

In one third (5 of 15) of the children diagnosed with Marfan syndrome, the disease was sporadic. When first examined, four (80%) of the five sporadic patients with cases had MR compared with three (30%) of of the 10 patients with familial cases. On echocardiographic examination, ARE and MVP were found to be similar in both groups. The mean paternal age for sporadic cases was 34.4 years (range, 29 to 38 years), whereas the mean paternal age at the time of birth of familial cases was 26.3 years (range, 19 to 33 years).

Four patients with ARE (patients 8, 9, 10, and 19) were treated with propranolol for an average of 4.2 years. One patient (patient 8) showed no further increase in the aortic root diameter for 1 year, another patient (patient 9) showed no increase for 5 years, and a third patient (patient 10) showed no increase for 3 years. None of these three patients experienced left ventricular enlargement. The fourth patient (patient 19) showed left ventricular enlargement because of preexisting mild hypertension due to renal failure, but his aortic root diameter did not increase during a 2.5-year follow-up.

COMMENT

Marfan syndrome is usually suspected when children with a marfanoid appearance are referred for medical evaluation. The presence of associated cardiac abnormalities such as mitral valve regurgitation and ARE may raise a strong suspicion of Marfan syndrome. These cardiac features, however, are not specific or certain evidence of the diagnosis in the absence of a positive family history or other system involvement. Three of our patients were found to have other diagnoses in spite of a marfanoid appearance and characteristic cardiac findings. Patient 17, with neurofibromatosis, in fact had MVP and myopia and, therefore, based on meeting three of four positive criteria, was diagnosed as having Marfan syndrome. Myopia and MVP, however, although common in Marfan syndrome, are relatively weak diagnostic features because of their high frequency in the general population. Therefore, the ultimate classification of marfanoid children and a definitive diagnosis of Marfan syndrome will likely await the discovery of the primary genetic defect or associated molecular markers. In the meantime, detailed clinical assessments must serve to distinguish other disorders with concomitant marfanoid features.

The cardiovascular system was involved in all 20 children with marfanoid features, of whom 15 (75%) were thought to have Marfan syndrome. Whether this high association of cardiac findings and marfanoid appearance is due to a selected sample will require prospective or population-based studies to evaluate. In any case, marfanoid children may have potentially serious cardiac findings and will require the same careful follow-up as those diagnosed with Marfan syndrome.

In the subset of the 15 children with diagnosed Marfan syndrome, pectus deformity and myopia were common findings. Similar observations were made by Geva et al.[9] In contrast, however, ectopia lentis was present in only 30% of our children, compared with 60% of those studied by Geva et al.[9] The absence of ectopia lentis, therefore, does not exclude the diagnosis. It is of interest, however, that we did not find ectopia lentis in any marfanoid child who was not thought to have Marfan syndrome.

In one third of our children diagnosed with Marfan syndrome, the disease was sporadic and had a greater frequency of MR than in the familial cases. The sporadic patients also had older fathers. These findings are consistent with previous reports[1,2] showing that in one third of patients with Marfan syndrome, the disease is sporadic and that sporadic cases tend to be more severely affected.[1] It has also been previously reported that there is a higher frequency of MR in sporadic cases than in familial ones (75% vs 29.4%).[9] The advanced paternal age of sporadic cases is related to the increased chance of new mutations.[10]

There are few reports of the cardiac manifestations of Marfan syndrome in young children that include echocardiography.[9,11-13]

These studies and our data indicate that aortic dilatation may appear early in life, precede the appearance of AR probably in all cases, and not be detectable by clinical examination or chest roentgenography. Aortic root enlargement was found in 12 (80%) of our 15 patients with Marfan syndrome. Only three patients had AR detected by auscultation. Moreover, the aortic root progressively enlarges throughout childhood, a process that, when accelerated, may lead to AR before adolescence. Involvement of the mitral value is almost as common as ARE in Marfan syndrome and may be severe in children.[14-20] In a longitudinal review of 120 patients younger than 22 years, mitral valve dysfunction in Marfan syndrome presented as MVP and, as opposed to idiopathic MVP, progressed clinically in about half.[21]

Therefore, periodic clinical and echocardiographic evaluation of children with Marfan syndrome is mandatory to establish the optimal time for surgical intervention. Gott et al[22] suggest elective aortic graft surgery when the aortic root diameter reaches 6 cm. Aortic root enlargement is progressive and most likely due to the strain of ventricular ejection; thus, chronic reduction in inotropy might retard the rate of ARE and prevent or delay complications.[23] In our study, none of the four patients treated with propranolol showed an increase in the aortic root diameter or experienced left ventricular enlargement. This finding is consistent with those of Pyeritz,[24] who suggested that long-term propranolol treatment reduces the rate of ARE and the development of severe complications in Marfan syndrome. Long-term, prospective, and controlled studies, however, are necessary to evaluate the effectiveness of this treatment in children.

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In Other AMA Journals

ARCHIVES OF PATHOLOGY & LABORATORY MEDICINE

College of American Pathologists–Centers for Disease Control Collaborative Study for Evaluating Reference Materials for Total Serum Cholesterol Measurements

Gary L. Myers, PhD; Don Schap; S. Jay Smith, MS, MIS; Gerald R. Cooper, MD, PhD; Alfred E. Hartmann, MD; Bryce Gilmore; C. Alan Suenram, PhD; David H. Ray (*Arch Pathol Lab Med.* 1990;114:1199-1205)

Differences in Expression of Cystic Fibrosis in Blacks and Whites

Susanna A. McColley, MD; Beryl J. Rosenstein, MD; Garry R. Cutting, MD

• The recent identification of the cystic fibrosis (CF) gene confirms that genetic heterogeneity occurs in CF. A three-base-pair deletion in exon 10 resulting in a loss of the phenylalanine residue at amino acid position 508 of the gene product, termed the *CF conductance regulator protein*, accounts for 70% of cases of CF in white subjects. However, this gene defect occurs in only 37% of affected blacks. Analysis of CF genes from American blacks has revealed a number of mutations, most of which are unique to that population. We therefore searched for potential differences in expression of CF between 24 black and 48 white patients with CF matched for birth date and gender. Black patients more frequently presented with only respiratory symptoms (38% vs 10%). Black patients had fewer hospitalizations for pulmonary exacerbations (2 vs 6.9), a better mean forced vital capacity (77% vs 62% of predicted), and higher chest roentgenogram scores (18.2 vs 14.4) than white patients. Complication rates were similar except for a higher incidence of hyponatremic dehydration (21% vs 2%) and peptic ulcer disease (13% vs 0%) in blacks. Survival time appeared to be longer in blacks, but the difference was not statistically significant. We conclude that phenotypic differences exist between black and white patients with CF, which may be due to the genetic heterogeneity between these two populations.

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Localization of the gene for cystic fibrosis (CF) to chromosome 7 was reported in 1985.[1-3] Before the discovery of the gene, several DNA markers were linked to the CF gene. Patterns of these markers, called haplotypes, were identified. It was discovered that the haplotype most highly associated with CF in white subjects was only weakly associated with CF in blacks, suggesting genetic heterogeneity between these populations.[4,5] The gene responsible for CF was recently identified and is predicted to encode a 1480-amino acid protein termed the *CF conductance regulator protein.*[6-8] One common mutation, resulting in a loss of the phenylalanine residue at amino acid position 508 of the CF conductance regulator protein (delta F508), accounts for 70% of CF gene mutations in whites but for only 37% of CF gene mutations in American blacks.[8-10] This confirms that the incidence of CF in American blacks is not due to genetic admixture alone. Analysis of CF genes from American blacks has revealed a number of mutations, most of which appear to be unique to that population.[10]

Cases of CF have been reported in blacks since 1954.[11] Early reports suggested that the prognosis for blacks was poor, with all patients dying by the age of 6 months in one retrospective study,[12] and 75% dying before the age of 5 years in another.[13] A subsequent study found that black patients experienced more severe gastrointestinal manifestations but less severe respiratory disease than white patients and had a longer survival.[14] Others have not observed differences in the clinical course.[15,16]

Since the genotypes of most American black and white patients differ, we compared the clinical course of patients from these two groups to detect any differences in phenotype. We reviewed the presenting features, clinical course, and survival of patients with CF followed up at The Johns Hopkins Hospital (JHH), Baltimore, Md.

PATIENTS AND METHODS

The charts of all 24 black patients with CF seen at JHH from 1971 to 1986 and 48 matched white patients were reviewed. The diagnosis of CF was based on characteristic clinical features and two positive pilocarpine iontophoresis sweat tests. Fourteen of the black patients were subjects of haplotype and subsequent gene analysis, reported previously.[5,10]

Two white patients with CF were selected for each black patient. Matching was by birth date and, when possible, by gender. Birth dates of the white patients were within 10 months of those of the black patients. In four cases, there were no white patients of the same gender born within 10 months, or charts could not be located. For these cases, opposite-sex patients matched for birth date were selected.

Patients were seen in the JHH CF clinic at 3-month intervals. One physician (B.J.R.) the CF center director, coordinated care for all subjects and was chiefly responsible for patient treatment decisions. Respiratory tract cultures and measurements of height and weight were obtained at each visit. Chest roentgenograms were obtained at least yearly, and more frequently if clinically indicated. Spirometry was done at each visit on patients who could perform forced expiratory maneuvers. Results were compared with predicted values calculated according to height, gender, and race.[17,18] Routine management included chest physiotherapy and aggressive nutritional support. Use of pancreatic enzymes, antibiotics, and bronchodilators was individualized according to the results of clinical, roentgenographic, and laboratory findings.

Outpatient and inpatient medical records were reviewed for clinical data, including

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From the Eudowood Division of Pediatric Respiratory Sciences (Drs McColley and Rosenstein) and the Division of Pediatric Genetics (Dr Cutting), Department of Pediatrics, The Johns Hopkins University School of Medicine, Baltimore, Md. Dr McColley is a fellow of the American Lung Association of Maryland, Inc.

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Reprint requests to Department of Pediatrics, The Johns Hopkins Hospital, CMSC 1-141, 600 N Wolfe St, Baltimore, MD 21205 (Dr McColley).

sweat chloride concentrations, presenting features, diagnostic delay, colonization with *Pseudomonas aeruginosa*, use of pancreatic enzymes and bronchodilators, complications, hospitalizations, and growth measures. Diagnostic delay was defined as the interval between the onset of symptoms suggestive of CF and the first positive sweat test. The patients' most recent chest roentgenograms were reviewed by one of us (B.J.R.), who was unaware of the patient's identity at the time of the review. Roentgenograms were scored by the method of Brasfield et al[19]; 25 represents a maximum score, with points subtracted for air trapping, linear markings, nodular-cystic lesions, large lesions, and general severity. Roentgenograms were available for 23 of 24 black patients and 42 of 48 white patients. Data on survival and withdrawal from the clinic were compiled, and life-table analyses and survival curves were generated using standard techniques.[20]

To determine whether the matched white patients were representative of our entire white population with CF, we abstracted data on presenting features for the 206 white patients with CF followed up at JHH between 1971 and 1986 who were not included in the study population.

Statistical analysis was performed using Mann-Whitney *U* tests for data that were not normally distributed and Fisher's Exact Test for comparing clinical data. Survival curves were compared using the log likelihood test. A *P* value of .05 was considered significant.

RESULTS

The presenting features of the 24 black and 48 matched white patients are given in Table 1. Black patients were diagnosed later and had a longer diagnostic delay, but the differences were not significant. Black patients were more likely to present with only respiratory symptoms.

Data related to the clinical course of the black and matched white patients are given in Table 1. Mean follow-up was 8.0 years for black patients and 10.9 years for white patients, with a total follow-up of 192 and 501 patient-years, respectively. Mean age at last follow-up was 12.5 years for black patients and 13.3 years for white patients. Three white and four black patients were unavailable for follow-up at a mean age of 11.7 and 8.4 years, respectively. Black patients had fewer total hospitalizations, but there was no difference in the number of hospital days per year of follow-up. This discrepancy was due to two black patients who had prolonged hospitalizations for respiratory symptoms early in life and who died at ages 3 years 11 months and 5 years, respectively. Age at first colonization with *P aeruginosa*, as well as colonization rates, were similar for both groups. Pulmonary function testing showed no difference in forced expiratory volume in 1 second, but a higher mean forced vital capacity in blacks. Significantly more white patients received bronchodilator therapy because of symptoms and clinical findings consistent with reactive airways disease. Chest roentgenogram scores were significantly higher in blacks, indicating less severe roentgenographic changes. Age at most recent chest roentgenogram and pulmonary function testing was similar for both groups. The percentage of subjects who took pancreatic enzyme supplements was the same for both groups. There was no difference in the incidence of growth failure, defined as height or weight less than the fifth percentile for age.

The incidence of nasal polyps, hemoptysis, rectal prolapse, diabetes mellitus, pneumothorax, cirrhosis, and distal intestinal obstruction syndrome (meconium ileus equivalent) was similar in both groups. Blacks had a significantly higher incidence of hyponatremic dehydration and of peptic ulcer disease (Table 1).

Characteristics at presentation of the 206 white patients not included in the study were similar to those of the 48 white patients selected for study, except that more of the nonstudy patients had presenting features other than meconium abnormalities or gastrointestinal and respiratory symptoms (Table 2). Most of these patients were asymptomatic siblings of patients with CF; others had a variety of manifestations, including anemia and edema, fat-soluble vitamin deficiencies, liver disease, or salty taste.

Survival curves of the black and white study patients are shown in the Figure. The configuration is similar to the curves of Stern et al.[14] Although black survival appears to be longer, there were few deaths and a relatively large number of patients unavailable for follow-up, and the difference was not statistically significant.

Table 1.—Characteristics, Clinical Course, and Complications in 24 Black and 48 White Patients with CF*

	Black	White
Characteristics		
Sex		
M	12 (50)	28 (58)
F	12 (50)	20 (42)
Family history	2 (8)	14 (29)†
Sweat chloride, mmol/L	108 (27)	100 (32)
Mean (SD) age at diagnosis, mo	58 (80)	24 (42)
Diagnostic delay, mo [mean (SD)]	34 (40)	16 (31)
Features at presentation		
Meconium abnormality‡	6 (25)	10 (21)
GI symptoms	3 (13)	7 (15)
Respiratory symptoms	9 (38)	5 (10)§
Both GI and respiratory symptoms	5 (21)	21 (44)
Other	1 (4)	5 (10)
Clinical course		
Mean (SD) hospitalizations	2.0 (3.5)	6.9 (12.6)†
Hospital d/y [mean (SD)]	6.1 (10.6)	6.6 (10.8)
Bronchodilator use	5 (21)	42 (88)†
Pancreatic enzyme use	21 (88)	42 (88)
Colonization with *Pseudomonas aeruginosa*		
Cumulative	15 (63)	36 (75)
Mean (SD) age colonized, y	5.8 (5.6)	5.7 (5.9)
FEV_1, % predicted [mean (SD)]	64 (27)	52 (32)
FVC, % predicted [mean (SD)]	77 (18)	62 (29)†
FEV_1:FVC [mean (SD)]	0.72 (0.19)	0.62 (0.16)
Mean (SD) age at last PFT, y	16.2 (5.2)	16.6 (6.1)
Mean (SD) chest roentgenogram score	18.2 (3.2)	14.4 (5.6)§
Mean (SD) age at last chest roentgenogram, y	15.7 (5.6)	12.5 (8.1)
Height <5th percentile	8 (33)	12 (25)
Weight <5th percentile	9 (38)	20 (42)
Complications		
Nasal polyps	4 (17)	5 (10)
Hemoptysis	3 (13)	6 (13)
Pneumothorax	1 (4)	4 (8)
DIOS	3 (13)	7 (15)
Diabetes mellitus	1 (4)	3 (6)
Cirrhosis	0 (0)	2 (4)
Peptic ulcer	3 (13)	0 (0)†
Hyponatremic dehydration	5 (21)	1 (2)‡

*CF indicates cystic fibrosis; GI, gastrointestinal; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; PFT, pulmonary function testing; and DIOS, distal intestinal obstruction syndrome. Values are number (percent) or mean (SD).

†*P*<.05.

‡Meconium abnormality includes meconium ileus or meconium plug syndrome.

§*P*<.01.

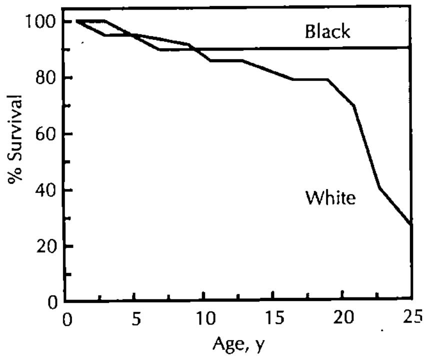
Table 2.—Characteristics of 206 White Patients with CF Not Studied*

	Value
Characteristics	
Age at diagnosis, mo	31±60
Diagnostic delay, mo	25±55
Features at presentation	
Meconium abnormality†	28 (14)
GI symptoms only	20 (10)
Respiratory symptoms only	27 (13)
Both GI and respiratory symptoms	77 (37)
Other	54 (26)‡

*CF indicates cystic fibrosis; GI, gastrointestinal. Values are mean±SD or number (percent).

†Meconium abnormality includes meconium ileus or meconium plug syndrome.

‡$P<.05$ compared with white patients studied.



Survival of 24 black and 48 white patients with cystic fibrosis. The difference in survival is not statistically significant.

COMMENT

Cystic fibrosis is the most common lethal genetic disease in the white population, with an incidence of approximately 1:2200.[21-24] The incidence is lower in blacks, estimated at 1:17 000.[12] In 1987, among 14 026 patients reported to the Cystic Fibrosis Foundation registry, 2.9% were black.[25] At the JHH CF center, 8% of patients are black, possibly reflecting the racial composition of our referral area. This has allowed us the opportunity to study a larger group of black patients with CF than has been previously reported. We chose to compare their clinical course with that of white patients matched for birth date to eliminate confounding factors related to changing standards of care over time.

Significantly more black than white patients had only respiratory symptoms at diagnosis. This differs from the findings of Kulczycki et al[13] who found both respiratory and gastrointestinal symptoms at diagnosis in most blacks and from those of Stern el al[14] who found a preponderance of gastrointestinal symptoms at diagnosis in blacks. Our findings are similar to those of Prapphal et al[26] who found only respiratory symptoms at diagnosis in 40% of black patients with CF. The finding that fewer black patients had gastrointestinal manifestations at diagnosis, but that an equal percentage required pancreatic enzyme supplements, suggests that the onset of pancreatic insufficiency may be delayed in this population.

Complications were similar in our black and white patients except for the higher incidence of hyponatremic dehydration and peptic ulcer disease in blacks. Hyponatremic dehydration occurs in CF secondary to excessive losses of sodium and chloride in the sweat. The higher frequency of dehydration in black patients cannot be explained by a difference in sweat electrolyte concentrations, which were similar in both groups. We are not aware of data regarding comparative sweating rates in blacks and whites. It is possible that the higher incidence of hyponatremic dehydration in blacks was secondary to socioeconomic factors such as less use of air conditioners. Peptic ulcer disease has been previously reported as a complication in adolescent blacks with CF.[27] The 13% incidence is much higher than expected for the general pediatric and young adult population.[28-30] Unlike Stern et al,[14] we did not observe a higher incidence of distal intestinal obstruction syndrome in our black patients.

Our results suggest that respiratory disease is milder in black patients with CF. Although *P aeruginosa* colonization rates were similar between black and white patients, blacks had higher forced vital capacities, better chest roentgenogram scores, less bronchodilator use, and fewer hospitalizations for pulmonary exacerbations. Chest roentgenogram scores have been shown to correlate with clinical scores, pulmonary function, and morbidity.[19] Airway hyperreactivity has been shown to correlate with more rapid respiratory deterioration.[31] Although the retrospective nature of our study did not allow for formal testing of airway reactivity, it is likely that those patients who took bronchodilators had some component of reversible airways obstruction.

Our data suggest that survival may be better in blacks; this has been suggested by Stern et al[14] and by data from the Cystic Fibrosis Foundation.[32] However, a larger series with longer follow-up will be necessary to analyze this trend further.

Prognostic indicators have been previously reported in patients with CF.[33-38] Early *Pseudomonas* colonization, female gender, pancreatic insufficiency, and presentation with pulmonary manifestations suggest a worse prognosis, while diagnosis at an early age has been associated with less rapid progression of pulmonary disease.[39] These factors do not account for the milder pulmonary course in our black patients. Black patients were older at diagnosis, more frequently presented with pulmonary manifestations, and had a sex ratio, incidence of pancreatic insufficiency, and mean age at first *Pseudomonas* colonization similar to those of our white patients.

Cystic fibrosis is a disease with marked phenotypic heterogeneity.[40] Genetic heterogeneity between black and white patients with CF may account for the observed differences in the clinical course. Analysis of genes from a number of black patients, including 14 who were a part of this study, showed a high frequency of non–delta F508 mutations.[10] Genotypic variation may produce a different, perhaps milder, phenotype in some black patients than that commonly observed in the white population. Because a number of mutations were found and only a relatively small number of subjects had gene analysis, we were unable to correlate specific gene mutations with disease severity. Previous reports have suggested that different haplotypes may be associated with milder disease in other populations with CF[41,42] and that pancreatic sufficiency in white patients with CF may be the result of multiple different mutations of the CF gene.[8,43] The success in identifying the most common gene mutation resulting in CF should allow investigators to continue defining other gene mutations, further delineating genetic differences between populations. Larger, multicenter studies of black patients with CF may then be useful for ırther characterizing differences in linical course and survival.

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Cat-Scratch Disease

Acute Encephalopathy and Other Neurologic Manifestations

Hugh A. Carithers, MD, A. M. Margileth, MD

• Seventy-six patients with neurologic complications of cat-scratch disease are discussed. Encephalopathy occurred in 61, while 15 had either cranial or peripheral nerve involvement. The average age of the patients with encephalopathy was 10.6 years (range, 1 to 66 years), and almost twice as many males as females were affected in contrast to patients with uncomplicated cat-scratch disease, in which the ratio was almost equal. Fever was not documented in 50% of patients with encephalopathy and only 26% had temperatures higher than 39°C. Convulsions occurred in 46% and combative behavior in 40%. Lethargy with or without coma was accompanied by variable neurologic signs. Results of laboratory studies, including imaging of the central nervous system, were inconsistent and nondiagnostic. Biopsy tissue from 14 patients showed histopathologic findings compatible with cat-scratch disease. The "English-Wear bacillus" was demonstrated by the Warthin-Starry stain in 10 of 14 skin or lymph node specimens. Of the 15 patients without encephalopathy, two children with facial nerve paresis displayed cranial nerve symptoms and/or signs, 10 patients had cat-scratch disease neuroretinitis, and three women had peripheral neuritis. All 76 patients recovered within 12 months; 78% recovered within 1 to 12 weeks. There were no neurologic sequelae. Treatment consisted of control of convulsions and supportive measures. Commonly used antibiotics administered to more than half of the patients were apparently ineffective.

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Cat-scratch disease (CSD) is a universally encountered infection caused by a pleomorphic gram-negative bacillus.[1] Its most serious clinical feature is an encephalopathy that was first described by Stevens[2] 2 years after the first description of CSD by Debre et al.[3] A review of the world literature in 1967 revealed 20 patients with diverse central nervous system manifestations.[4] Lyon[5] collected 18 patients from the English literature in 1974 and added a case of his own. In 1986, Lewis and Tucker[6] described 38 cases with diverse neurologic manifestations, including those previously mentioned, and added two new patients with encephalopathy; four of these patients had predominantly myelopathic involvement without encephalopathy.

Cat-scratch disease encephalopathy (CSDE) ranks with chicken pox, herpes simplex, Lyme disease, Rocky Mountain spotted fever, and Kawasaki disease in frequency of neurologic complications. This coincides with a recent reduction in the number of patients with measles and mumps encephalitis due to vaccination, and with the increasing rarity of insect-borne encephalitis.[7] It is not known whether the CSDE is due to direct invasion of the brain by the bacillus or some other mechanism such as cerebral vasculitis.[8] We describe herein the course, unique clinical features, and outcomes of CSDE in 61 patients, and describe the cranial and peripheral nerve involvement in an additional 15 patients.

PATIENTS AND METHODS

All patients presented or were reported to us between 1959 and 1987, a period in which we observed approximately 3000 patients with CSD.[9,10] We observed 25 of the 76 patients in this report; the remaining 41 with encephalopathy were reported to us by their physicians, who supplied details of the clinical course, laboratory findings, and follow-up. We provided antigen for skin testing to confirm the diagnosis.

The diagnosis was confirmed in all 76 patients when three of the following four criteria were met: (1) single or regional lymphadenopathy without obvious signs of cutaneous or throat infection; (2) contact with a cat, usually an immature one; (3) detection of an inoculation site; and (4) a positive skin test result for CSD. The finding of the bacteria causing CSD might be considered a single valid criterion; however, this mode of diagnosis is almost never necessary, is unreliable except in experienced hands, and requires general anesthesia for most patients. We, therefore, do not include it as a criterion. One of us (A.M.M.) usually includes the elimination of other causes of lymphadenopathy as a criterion for diagnosis, but routine laboratory work is inconsistent and most cases can be readily diagnosed without it.

The age range of the 61 patients with CSDE was 1 to 66 years (mean, 10.6 years). In a previous report of 34 patients with CSDE, the range was 3 to 48 years (mean, 13 years).[6] The Table compares the ages of these two combined groups (95 patients) with those of 1200 patients with CSD described by Carithers.[9] Of the 95 patients with CSDE, 37% were female and 63% male. In two studies of uncomplicated CSD, the male-female ratio showed only a slight increase in males (54% and 56%).[9,10] The patients with CSDE resided in 15 states representing all geographic areas delineated for reporting purposes by the United States Public Health Service. Of the 15 patients without encephalopathy seen between 1972 and 1987, five were males and 10 females, and the age range was 1.5 to 54 years (mean, 21 years).

RESULTS

Clinical Data

The manner in which our data were collected does not provide an accurate

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From the Jacksonville Health Education Program, University of Florida (Dr Carithers), and Department of Pediatrics, Uniformed Services University of the Health Sciences, Bethesda, Md (Dr Margileth).

Reprint requests to 2121 Park St, Jacksonville, FL 32204 (Dr Carithers).

Age Distribution of Patients With Cat-Scratch Disease (CSD)[9] and CSD Encephalopathy (CSDE)*

Age, y	Patients With CSD, % (n=1200)	Patients With CSDE, % (n=95)
1 to 6	41.0	20.0
7 to 12	42.0	48.0
13 to 18	7.3	17.0
≥18	9.7	15.0

*Patients with CSDE included 61 patients from rrent study and 34 from the study by Lewis and cker.[6]

stimate of the incidence of encephalop- hy in patients with CSD. However, it a rare complication. One of us exam- ed over 1800 patients and diagnosed nly three with CSDE, for an incidence 0.17%, while the other author .M.M.) included patients seen direct- or by consultation and diagnosed SDE in 31 of 1500 patients, for an inci- ence of 2%. On a percentage basis, en- phalopathy occurs more commonly mong adolescents and adults.

The interval between onset of CSD nd the first sign of central nervous sys- em involvement is impossible to deter- ine accurately from the data in the resent study. Since CSD is character- tically benign, often undiagnosed, it akes the determination of its onset uestionable. The histories of these pa- ents allowed us to conclude that en- phalopathic complications may occur om a few days to as long as 2 months fter detection of illness, usually in the rm of a mildly tender lymphadenop- hy. It cannot be assumed that patients ho present with convulsions are at the nset of CSD. All three patients in this udy who presented in this manner had een infected for more than a week.

All patients had a history of cat con- ct, usually with an immature cat. All ut one patient had a positive cat- ratch skin test result and most had a egative tuberculin skin test result.

Fever was not a characteristic fea- ire; 30 (50%) had no recognized fever ith temperatures less than 38.3°C, 14 3%) had fever not exceeding 39°C, and 3 (26%) had fever between 39°C and 0°C. These closely approximate the ercentages seen in a previous study of 200 patients with CSD.[9]

The lymph nodes involved in the 61 atients were detected in approximately the same locations as in patients with typical CSD.[9,10] There were no indications suggesting that affected lymph nodes around the head and neck predisposed to central nervous system involvement.

Convulsions in 28 (46%) of 61 patients varied from mild twitching of extremities to status epilepticus of 3 to 4 hours' duration. One infant had generalized tonic-clonic seizures, each lasting 1 minute and occurring one to 21 times daily for 6 weeks. She was comatose for 7 weeks. Developmental delay and deafness both resolved after 8 months. No patient had absence seizures. Patients without convulsions may have depression of the central nervous system varying from lethargy to coma.

Transient combative behavior occurred in 24 (39%) of 61 patients who were comatose or semiconscious during the "recovery" phase of a convulsive episode, occasionally during the twitching phase and rarely in a quiet postictal state. The patients acted out by hitting, pushing away, and vocally protesting. This was typically provoked by parents as well as medical staff on touching the patient, especially around the head and neck. To our knowledge, this behavior with this frequency is undocumented in any other type of encephalopathy.

Of other signs and symptoms, headache, usually generalized and persistent, was the most common. Lethargy and malaise lasting 1 to many weeks were common, as is the case in uncomplicated CSD. Persistent ataxia lasting 1 to 8 weeks following the acute phase of encephalopathy was noted in four patients. Less common findings (occurring in only one patient each) were bilateral sixth nerve palsy, aphasia lasting several days, transient hemiplegia, and profound hearing loss lasting 8 months. We do not believe that the severity of CSD is related to development of encephalopathy. Confirming this impression, the presence and degree of elevation of fever are approximately the same in patients with uncomplicated CSD and in those with encephalopathic complications.

Laboratory and Other Studies

The cerebrospinal fluid findings in 51 patients were neither consistent nor characteristic. Sixteen (31%) patients had white blood cell counts of more than 5×10^6/L; the range was 5 to 33×10^6 and 70% to 100% were lymphocytes. Protein concentration was normal in 33 patients (65%) and ranged between 0.41 and 0.93 g/L in 18 (35%). Cerebrospinal fluid glucose was abnormally low in one patient. Routine cultures of cerebrospinal fluid were negative for aerobic, anaerobic, fungal and mycobacterial organisms. Peripheral blood counts in 60 patients were not helpful in diagnosis or prognosis. In 15 patients, the white blood cell count was more than 12×10^9/L, ranging from 12.2 to 37×10^9/L. Two patients had counts below 6×10^9/L. Elevated sedimentation rates occurred in 21 (46%) of 46 patients tested.

Computed tomographic scans performed on 33 patients were not diagnostic and were usually normal or revealed transient abnormalities. Electroencephalography performed during the acute phase of the disease showed background slowing consistent with encephalopathy in 36 (80%) of 46 patients. Follow-up electroencephalograms after 3 to 18 months were normal in all patients.

Cranial magnetic resonance imaging was performed on six patients, five of whom showed normal findings, but one patient had focal changes in the occipital area, also noted on the computed tomographic scan. Carotid arteriography performed on two patients showed normal results.

Fifty-nine of 60 skin tests with cat-scratch antigen had positive results.[11] One patient who was tested elsewhere had a questionable reaction. Another patient who did not undergo a skin test showed a positive reaction to Warthin-Starry stain on lymph node biopsy. Serologic tests for cytomegalovirus, Epstein-Barr virus, toxoplasmosis, and fungi; blood chemistries; cultures of blood or cerebrospinal fluid; tests for mononucleosis; toxic screens; tuberculin tests; and skull films showed normal findings.

Pathologic Findings

Histopathologic study was performed on tissue from 14 patients by Wear et al,[1] who discovered the cat-scratch bacillus in 1983. Biopsies of 13 lymph nodes, two primary skin inoculation lesions, and one conjunctival granuloma were performed. Stellate or inflammatory granulomas were detected in six lymph nodes, and focal or multiple areas of necrosis with vasculitis were found in seven patients' nodes or skin. The cat-scratch bacillus was detected by the Warthin-Starry silver stain in 10 of the 14 patients. Only three specimens were unfixed and fresh enough for culture studies, and all results were negative.

Pathologic sections of nodes removed from patients with CSD may show abscesses and/or granulomas. These changes can occur in other diseases and are not diagnostic of CSD, but when both abscesses and granulomas are observed in the same specimen, the findings are consistent with CSD.

COMMENT

Diagnosis

Cat-scratch disease encephalopathy is readily diagnosed when signs and symptoms of central nervous system dysfunction develop during the course of CSD. In patients not identified as having CSD, a convulsion is usually the first symptom of CSDE.[9,11] Typical of this group was a 9-year-old boy who was brought to the emergency room with generalized convulsions and a temperature of 38°C. He was admitted to the intensive care unit and the convulsions were controlled after 30 minutes with diazepam. A spinal tap showed no abnormalities; a complete blood cell count showed a white blood cell count of 16×10^9/L, 72% of which were polymorphonuclear. Drug screening showed normal findings, as did biochemical studies, skull and chest roentgenograms, computed tomographic scan of the brain, and ultrasound study of the abdomen. The patient was initially examined by an emergency room physician, a pediatric resident, and two intensive care attending physicians. An electroencephalogram was normal. The patient was combative and unconscious throughout the next 12 hours, becoming more responsive but remaining querulous for 2 days. Twelve hours after admission, another resident found a large inguinal lymph node measuring 2×3 cm. A red papule, more firm than a mosquito bite, was found on the ankle on the same side as the lymphadenopathy. The presence of a 4-month-old kitten in the patient's home was established. The cat-scratch skin test showed positive results in 48 hours and the boy was discharged on the fifth hospital day, having entirely recovered. Follow-up for several months showed no residual effects of the illness.

Cat-scratch disease encephalopathy should be considered when a young patient presents with a sudden onset of coma and/or convulsions. One should probe for a history of cat exposure even though the parents and child deny such contact. Children may express denial due to feared parental disapproval or through forgetfulness. A thorough search should be made for lymphadenopathy and presence of a regional inoculation papule or conjunctival granuloma. An almost certain diagnosis of CSD can be made if these signs are found. The diagnosis of CSD can be confirmed if a cat-scratch skin test shows positive results at 48 to 72 hours.[11] Removal of the lymph node involved is rarely necessary.[12] The processing of biopsied tissue requires several or more days, compared with cat-scratch skin testing, which is more diagnostic.[8,9,11] Granulomatous or necrotic changes found in lymph nodes due to CSD are nonspecific.[1] Unless the organism causing CSD is found in the biopsy tissue, the study will not be conclusive. Special stains such as the Warthin-Starry stain are not available in most clinical laboratories and, at times, are difficult to interpret.[13]

Differential considerations include viral or Lyme encephalitis, drug intoxication, poisonings, bacterial infections such as meningitis, Rocky Mountain spotted fever, Kawasaki disease, and Reye's syndrome. The viral encephalitides seen in this country include those associated with common contagious diseases that are disappearing, except for varicella, herpes, arboviruses, and enteroviruses. Central nervous system involvement may rarely be encountered with acute disseminated encephalomyelitis, acute hemorrhagic leukoencephalopathy, granulomatous arteritis, and the so-called slow viruses—conventional and unconventional.[7]

Treatment

It is believed that antibiotics do not modify the course of CSD. This opinion was based on the observation that the lymph nodes involved often continue to enlarge or progress to suppuration despite the oral or intravenous administration of several commonly used antibiotics. Not included in this group of drugs are gentamicin sulfate and third generation cephalosporins.[13] Recently, Bogue and associates[14] reported that signs and symptoms of systemic CSD promptly disappeared in three acutely ill patients after intravenous treatment with gentamicin sulfate. We are not aware of any patient with CSDE being treated with intravenous gentamicin sulfate. However, in the severely ill patient, we recommend the intravenous administration of 5 to 7 mg/kg per day of gentamicin sulfate at 8-hour intervals.[14] Duration of treatment would be based on response and the knowledge that recovery from CSDE is usually prompt (4 to 14 days) in the natural course of the disease. Recently, Collipp[15] reported excellent response to trimethoprim-sulfamethoxazole in 11 patients with CSD.

In addition to the control of convulsions and respiratory support, the most important aspect in the treatment of patients with encephalopathy is to establish the diagnosis as quickly as possible. This might avoid extensive and unrewarding studies that will disturb the patient. During coma, we recommend supportive measures with appropriate nursing care and close observation of the patient.

Prognosis

There were no deaths in this series. Reports of seven deaths due to CSDE[4] did not meet our diagnostic criteria for the disease. Although it is often difficult to determine the exact duration of illness in childhood, we believe the acute phase of encephalopathy associated with CSD is usually short. Approximately two thirds of the patients recovered fully in 4 weeks and none showed evidence of encephalopathy after 1 year. Patients of all ages may complain of lethargy, headache, fatigue or weakness, and anorexia for several weeks or months. These symptoms also appear in uncomplicated CSD.[8,9,11]

Follow-up data ranging from 3 months to 22 years were available in all 61 patients in this series. Over 50% of patients were followed up for more than 2 years. To date, no lasting neurologic impairment due to CSDE developed in these 61 patients. This form of encephalopathy is probably the least hazardous of any caused by direct central nervous system infection or serious response of the central nervous system to infection or toxins.

Neurologic Symptoms and Signs in Patients With CSD Without Encephalopathy

Transient dysfunction of cranial and/or peripheral nerves occurred in 15 of 1471 patients with CSD observed by one of us (A.M.M.) during the last 15 years. Two children aged 18 months and 3 years had temporary facial nerve paresis (Bell's palsy) associated with CSD oculoglandular syndrome lasting 4 to 5 weeks. These patients have not been studied as exhaustively as have the patients with CSDE and some are still under observation. We are including them in this presentation to alert physicians to the recent recognition of peripheral nerve disease associated with CSD.

Three women aged 26, 27, and 54 years had peripheral neuritis lasting 1 to 4 months. The 26-year-old had unilateral paresthesia with a transient Babinski sign and leg edema associated with inguinal lymphadenitis lasting 4 weeks. The 27-year-old patient developed severe neuralgia and myalgia of the left shoulder shortly after the onset of lymphadenitis of the left anterior and posterior cervical chains. The paresthesia, myalgia, and adenopathy slowly resolved over 4 to 5 months. The 54-year-old woman was hospitalized for 2 months with severe headaches; facial, eye, parietal, and temporomandibular painful swelling; and multiple cat scratches with bilateral cervical lymphadenitis.[16] The neuralgia and cephalgia persisted for 6 weeks, during which results of multiple diagnostic studies were normal or nondiagnostic. Treatment with several antibiotics and prednisone was ineffective. A diagnosis of oculoglandular syndrome of Parinaud due to CSD was confirmed, and all symptoms and signs abated after 3 months.

Ten patients (seven adults, one adolescent, and two children) with neuroretinitis and CSD were observed during the past 3 years.[17] Each patient presented with a sudden onset of blindness in one eye associated with regional lymphadenitis and cat scratches. All 10 recovered slowly during 4 to 12 months with subsequent visual acuity of 20/20 to 20/50 in the affected eye. Therapy with several antibiotics and/or prednisone was apparently ineffective.

Since preparation of this article, we have been consulted concerning an additional 14 patients with probable CSDE. Although follow-up has been brief, their clinical courses were similar to those of the 61 patients described. Presentation of an exhibit by R. Sawyer, MD; J. Teahan, MD; and A. M. Margileth, MD, on CSD neuroretinitis at the annual meeting of the American Academy of Ophthalmology has led to an increasing number of diagnoses of this condition in widespread areas of this country.

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Surfactant Replacement Therapy in Respiratory Distress Syndrome

Meta-analysis of Clinical Trials of Single-Dose Surfactant Extracts

Halim M. Hennes, MD; Martha B. Lee, PhD; Alfred A. Rimm, PhD; Donald L. Shapiro, MD†

• Replacement therapy with surfactant extracts in premature infants with respiratory distress syndrome has been evaluated in several clinical trials. The results of individual trials do not provide conclusive evidence that administration of a single dose of surfactant improves morbidity or mortality. Meta-analysis is a statistical method to combine the results of such clinical trials, and combined analysis provides a means to overcome the problem of not being able to detect significant small differences in individual trials due to these small sample sizes. Seven clinical trials (277 patients treated with nonhuman surfactant extract and 263 controls) met the criteria for analysis; five outcome measurements (mortality, patent ductus arteriosus, pneumothorax, intraventricular hemorrhage, and bronchopulmonary dysplasia) were selected to estimate the treatment effect. The meta-analysis showed that a single dose of surfactant administered before the first breath or within 15 hours of birth significantly decreased the mortality rate (95% confidence interval = −0.19 to −0.03) and the risk of developing pneumothorax (95% confidence interval = −0.28 to −0.14) in infants with respiratory distress syndrome. Further clinical trials are needed to evaluate other aspects of surfactant replacement therapy in premature infants because inconsistent results were observed among the seven analyzed studies.

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Neonatal respiratory distress syndrome (RDS) is a major cause of morbidity and mortality in premature infants.[1] Continuing advances in the respiratory care of infants and animal studies provide evidence that deficiency of lung surfactant is the primary underlying cause of RDS.[1,2] In 1978, Adams et al[2] showed that surfactant replacement in premature lambs resulted in improved aeration and prevented atelectasis. In 1980, Fujiwara et al[3] reported that treatment with exogenous surfactant (an extract of bovine lung) improved oxygenation and reduced the need for ventilatory support in premature infants with severe RDS. Since then, several clinical trials have been undertaken to evaluate the efficacy of surfactant replacement therapy using various surfactant preparations in the treatment or prevention of RDS.[4-18] The individual results of this group of trials have not provided conclusive evidence that surfactant replacement significantly improves morbidity or mortality of premature infants. Differences in study design, type of surfactant and dose used, and delivery technique may explain the variability in the reported results.

Meta-analysis is a statistical method designed to analyze and combine results from different clinical trials.[19-21] The objective of such analysis is to obtain a stable estimate of treatment effect, examine variability between trials, and resolve the uncertainty of conflicting results.[20] Selected trials should be of like design, have a similar study population, use the same or similar therapy, and measure the same outcome variables. To evaluate the treatment effect of surfactant replacement therapy on morbidity and mortality of premature infants with RDS, we performed a meta-analysis of seven published randomized clinical trials that used a single dose of nonhuman surfactant extract.

MATERIALS AND METHODS

Selection of Trials

A computer search of the English language literature was performed on surfactant replacement therapy used between January 1975 and May 1989 in premature infants with RDS. The bibliographies of the articles obtained by computer search were also reviewed. All studies were reviewed by all investigators and only randomized, controlled trials that used a single dose of nonhuman surfactant extract administered within the first 24 hours after birth were selected for meta-analysis. Inclusion criteria included (1) randomized controlled trials; (2) single dose nonhuman surfactant extract administered either at birth or within the first 24 hours; and (3) documentation of outcome which included survival, development of patent ductus arteriosus, pneumothorax, intraventricular hemorrhage, and bronchopulmonary dysplasia.

Statistical Analysis

Data were abstracted from the selected trials by one investigator (H.M.H.) and reviewed by two additional investigators (M.B.L. and D.L.S.) in a blinded fashion. Disagreements were resolved by group consensus. To evaluate the constancy of treatment effect across studies, a test of homogeneity[22] (the Cochran's Q) was used. The rate difference (rate in the treatment group minus rate in control group) was calculated for each of the five selected outcomes in each study. Results of all trials were then combined using the method described by DerSimonian and Laird[19] that allows each study to have its own treatment effect and incorporate any among-study differences that may cause variability in treatment effect. The mean effect of treatment (combined rate differences) can be estimated by a weighted average of rate differences. A negative value of this estimate would indicate a benefit from treatment. The 95% confidence interval (CI) was calculated for the combined rate difference. When the 95% CI includes zero, it suggests that there is no statistically significant difference between treatment and control groups.

RESULTS

Sixteen clinical trials were located: two nonrandomized trials[3,4] were excluded, as were trials using synthetic surfactant[6,14] or human surfactant.[5,7,11] One duplicate report[9] and one trial[18] that included patients from a pilot study were excluded from the analysis. Seven randomized clinical trials[8,10,12,13,15-17] re-

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From the Departments of Pediatrics (Dr Hennes) and Biostatistics and Clinical Epidemiology (Drs Lee and Rimm), Medical College of Wisconsin and Children's Hospital of Wisconsin, Milwaukee, and the Department of Pediatrics (Neonatology) and Specialized Care Center of Research for Respiratory Distress in Neonates, University of Rochester (NY) Medical Center (Dr Shapiro).

†Dr Shapiro died October 15, 1989.

Reprint requests to Department of Pediatrics, Children's Hospital of Wisconsin, PO Box 1997, MS 756, Milwaukee, WI 53201 (Dr Hennes).

Table 1.—General Characteristics of Selected Trials

Source, y	No. of Patients		Average Gestational Age, wk		Average Birth Weight, kg		Blinded	Placebo	Total Dose, mg	Time of Administration, h
	Treatment	Control	Treatment	Control	Treatment	Control				
Enhorning et al,[8] 1985	39	33	27.4	27.2	976	974	Yes	Air	75-100	0*
Kwong et al,[10] 1985	14	13	26.7	26.2	971	892	Yes	Saline	90	0*
Gitlin et al,[12] 1987	18	23	29	29	1214	1214	No	Saline	100†	<8
Raju et al,[13] 1987	17	13	28.4	27.6	1119	1096	Yes	Saline	100†	<6
Kendig et al,[15] 1988	34	31	28.8	28.4	1057	996	Yes	Saline	90	0*
European,[16] 1988	77	69	28.8	28.4	1246	1182	No	No	200†	2-15
Horbar et al,[17] 1989	78	81	28.5	28.2	1119	1160	Yes	Air	100†	<8

*Zero hour indicates at birth.
†Dose in milligrams per kilogram.

Table 2.—Effect of Surfactant Replacement on the Outcome in the Selected Trials*

Study	Mortality, %		RD, %	PDA, %		RD, %	Pneumothorax, %		RD, %	IVH, %		RD, %	BPD, %		RD, %
	S	C		S	C		S	C		S	C		S	C	
Enhorning et al[8]	3	18	−15†	46	58	−12	15	33	−18	28	61	−33†	56	67	−11
Kwong et al[10]	7	14	−7	50	29	21	43	50	−7	36	28	8	43	64	−21
Gitlin et al[12]	17	26	−9	78	65	13	17	57	−40†	89	74	15	22	30	−8
Raju et al[13]	18	47	−29	71	23	48†	12	47	−35†	47	62	−15	24	92	−68†
Kendig et al[15]	29	29	0	27	16	11	9	23	−14	24	16	8	35	36	−1
European[16]	31	51	−20†	60	46	14	18	35	−17†	47	55	−8	16	26	−10
Horbar et al[17]	17	17	0	1	48	−7	10	30	−20†	24	25	−1	45	44	1

*RD indicates rate difference; PDA, patent ductus arteriosus; IVH, intraventricular hemorrhage; S, surfactant group; C, controls; and BPD, bronchopulmonary dysplasia.
†Indicates that the results were statistically significant ($P<.05$).

Table 3.—Results of Cochran's Q Test of Homogeneity

Outcome*	Q	*P* Value
Death	6.57	.36
PDA	13.58	.03
Pneumothorax	3.86	.69
IVH	11.55	.07
BPD	24.29	.001

*PDA indicates patent ductus arteriosus; IVH, intraventricular hemorrhage; and BPD, bronchopulmonary dysplasia.

mained for the meta-analysis that included 277 infants treated with surfactant and 263 controls. The general characteristics of these trials are summarized in Table 1. There were no significant differences in gestational age or birth weights among those in the selected trials. All studies were randomized; five were blinded and six were placebo controlled. Surfactants were various bovine surfactant extracts in six studies and porcine in one[16] instilled into the lungs as a single dose. The lowest total dose used was 75 mg/kg[8] and the highest dose was 200 mg/kg.[16] Surfactant was administered before the first breath in three trials[8,10,15] and within 15 hours of birth in four trials.[12,13,16,17]

Table 2 summarizes the occurrence rates and risk differences for each outcome during the neonatal period in these trials. Although the rate difference for mortality ranged from 0% to −29%, only two studies[8,16] reported a significant decrease in mortality rate among the treatment group. For patent ductus arteriosus, the risk difference was −12% to 48%. Raju et al[13] found significantly fewer cases of patent ductus arteriosus in the surfactant group. Four trials[12,13,16,17] indicated that pneumothorax was observed less frequently in treated infants (rate difference, −7% to −40%). Surfactant treatment was also associated with statistically significant decreases in the occurrence rate of intraventricular hemorrhage in one trial[8] and the development of bronchopulmonary dysplasia in another.[13] The test of homogeneity (Cochran's Q) for treatment effect indicated lack of homogeneity across the studies for patent ductus arteriosus and bronchopulmonary dysplasia; hence, we used the method described by DerSimonian and Laird[19] that estimates the magnitude of heterogeneity and assigns a greater variability to the estimate of overall treatment effect to account for such heterogeneity (Table 3). Results of the combined analysis are summarized in Table 4. The combined rate differences for four of the five outcomes (mortality, pneumothorax, intraventricular hemorrhage, and bronchopulmonary dysplasia) were

Table 4.—The Combined Analysis of Treatment Effect for All Selected Trials*

Diagnosis	No. of Events/No. of Patients (%) Treatment	No. of Events/No. of Patients (%) Control	Treatment Effect	Treatment 95% CI	*P* Value
Death	55/277 (20)	78/263 (30)	−0.105	−0.19/−0.03	.01
PDA	135/277 (49)	117/263 (44)	0.073	−0.06/0.2	.26
Pneumothorax	43/277 (16)	98/263 (37)	−0.214	−0.28/−0.14	.0001
IVH	103/277 (37)	112/263 (43)	−0.051	−0.16/0.06	.35
BPD	95/277 (34)	115/263 (44)	−0.062	−0.14/0.03	.11

*PDA indicates patent ductus arteriosus; IVH, intraventricular hemorrhage; BPD, bronchopulmonary dysplasia; and CI, confidence interval.

negative in the direction of a treatment benefit. Only two of those differences, however, were statistically significant. For mortality, the combined rate difference was −0.105 and the corresponding 95% CI was −0.19 to −0.03 ($P=.01$). For pneumothorax, the combined rate difference was −0.214 and the corresponding 95% CI was −0.28 to −0.14 ($P=.0001$).

COMMENT

When performing meta-analysis, the selected trials should be randomized, placebo controlled, double blind, evaluate the same therapy in a comparable group of patients, and evaluate the same outcome variables. Of the seven selected clinical trials, two were not blinded[11,15] and one used no placebo.[16] However, all trials used objective outcome measurements (arterial blood gas values, ventilator requirements, etc) to determine treatment benefit. Accordingly, it is unlikely that the results were subject to observer bias. While no placebo was used in the collaborative European study, both treatment and control groups were subjected to the same protocol. To avoid the variability in reporting the results of pulmonary functions among these trials, we selected five binary outcomes to measure the treatment effect.

We were unable to determine from the available data if a specific surfactant dose or the time of administration significantly affected the observed results. Currently, the dose is based on the available theoretical data that 100 mg/kg will cover the entire lung surface, and we have no knowledge regarding the number of doses that should be given to maintain a stable physiological surfactant level. Shapiro et al[9] demonstrated that using multiple doses of surfactant significantly improved the survival rate among a high-risk group of infants. The timing of surfactant administration does not appear to be crucial since we observed no consistent difference between the trials that administered surfactant before the first breath and those that delayed administration for several hours. One disadvantage in administering surfactant prior to the first breath is the possibility of giving it to infants who do not need it, which may bias the observed results.

The detection of a statistically significant decrease in mortality rate and pneumothorax suggests that a single dose of nonhuman surfactant extract administered before the first breath or within 15 hours of birth to premature infants with RDS is beneficial. Leviton et al,[23] in a recent review, examined the association between RDS and the development of intraventricular hemorrhage using the results of the surfactant replacement trials. They concluded that these trials provided no evidence that surfactant replacement lowered the incidence of intraventricular hemorrhage. Therefore, further clinical trials are needed to evaluate specific aspects of surfactant replacement therapy such as repeated dosing, time of administration, potency and safety of various surfactants, and differences in response to surfactant by different patients.

Frances Sommer provided assistance in the preparation of the manuscript.

This article is dedicated to the memory of Donald L. Shapiro, MD.

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Gallstones in Children

Characterization by Age, Etiology, and Outcome

Shimon Reif, MD; Daniel G. Sloven, MD; Emanuel Lebenthal, MD

• Fifty children and adolescents were found to have gallstones at Children's Hospital of Buffalo (NY) during a period of 10 years. The mean (±SD) age was 12.2±6.2 years, with 21 boys and 29 girls. The majority of patients could be categorized into four groups: hemolytic disease (18 patients), parenteral nutrition (eight patients), adolescent pregnancy (seven patients), and idiopathic (10 patients), while seven patients had a variety of other etiologies. Right upper quadrant pain was the most common symptom (32 patients), followed by jaundice (15 patients), vomiting (13 patients), and nonspecific abdominal complaints (13 patients). Ten patients presented with jaundice and underlying hemolytic disease; seven patients were asymptomatic. Clinical presentation was found to vary with age and factors associated with the development of gallstones. Ultrasonography was the mode of diagnosis in 48 patients. Cholecystectomy was performed in 36 patients. In contrast to gallstones in adults, after exclusion of the patients with adolescent pregnancy, there was no female predominance. Pancreatitis was the most common complication, occurring in 8% of the patients; cholecystitis and cholangitis were absent.

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Gallstones have been regarded as an uncommon problem in children.[1-5] Reports since the advent of ultrasonography have identified groups of children not previously known to be at risk for gallbladder disease, such as patients with spinal injury and spinal surgery,[6,7] immunodeficiency,[8] and parenteral nutrition.[9] In this study, we discuss all patients having gallstones diagnosed at Children's Hospital of Buffalo (NY) from 1979 to 1989 to determine the clinical presentation, method of diagnosis, and modality of treatment in regard to the different age groups and factors associated with the development of gallstones.

PATIENTS AND METHODS

All charts of inpatients and outpatients with gallstones diagnosed radiographically or surgically at Children's Hospital of Buffalo from 1979 to 1989 were reviewed. Sonographic diagnosis of gallstones was based on the presence of mobile echogenic foci in the gallbladder lumen or in the region of the gallbladder fossa. Acoustic shadowing was not required for sonographic diagnosis because it is not always present when the foci are small.[10] Roentgenographic diagnosis of gallstones required calcifications in the right upper quadrant to be present in more than one view. Patients with previous biliary tract surgery, acalculus cholecystitis, and biliary tract disease without proven gallstones were excluded from our study.

Fifty patients met the criteria of the study. Patients were characterized by age, associated conditions, clinical presentation, laboratory studies, method of diagnosis, therapy, and outcome. A univariate analysis was conducted looking for a correlation between age, race, sex, clinical presentation, laboratory studies, therapy, and factors associated with gallstones by χ^2 analysis.

RESULTS

Fifty children with gallstones were identified at Children's Hospital of Buffalo from 1979 to 1989 with ages ranging from prenatal to 20 years. The mean (±SD) age at presentation was 12.2±6.2 years, with 21 boys and 29 girls. There were 29 whites, 17 blacks, and four Hispanics.

The age distribution is presented in the Figure. The tendency toward female predominance was noted only after 15 years of age. Diagnosis was most frequent after age 15 years; however, 8 patients were 5 years old or less. Conditions associated with the development of gallstones are shown in Table 1. Several of our patients had more than one associated factor. The majority of the patients could be categorized in one of four main groups: hemolytic disease (18 patients), parenteral nutrition (eight patients), adolescent pregnancy (seven patients), and idiopathic (10 patients). Seven patients who were not included in the four main groups had a variety of other etiologies.

Clinical presentations and the relationship between age and clinical presentation are shown in Table 2. While right upper quadrant pain was the most common symptom in 32 patients, 13 patients had nonspecific abdominal symptoms, including poorly localized abdominal pain, nausea, and chest pain; only one patient had fever. Seven patients were asymptomatic, including one patient diagnosed in utero by a routine maternal ultrasound study. The majority of patients had more than one symptom.

Right upper quadrant pain predominated in patients ages 6 years and older. No patients less than 6 years old presented with jaundice. Fatty food intolerance was observed only in patients older than 6 years old, and asymptomatic presentations predominated in younger patients. Nonspecific abdominal pain and vomiting showed no specific age distribution.

Ultrasonography was used to diagnose 48 patients. Other diagnostic methods included plain films (for four patients), abdominal computed tomography (for three patients), and oral cho-

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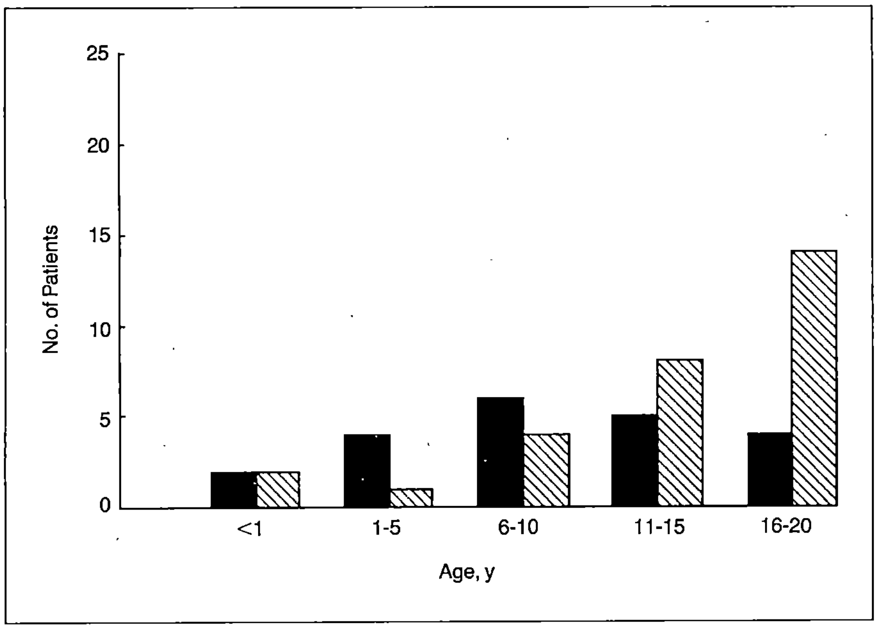
From the Division of Gastroenterology and Nutrition and Colucci Memorial Liver Research Center, Children's Hospital of Buffalo (NY) (Dr Reif); the Department of Pediatrics, St John's Mercy Medical Center, St Louis, Mo (Dr Sloven); and the Department of Pediatrics, Hahnemann School of Medicine, Philadelphia, Pa (Dr Lebenthal).

Reprint requests to Department of Pediatrics (402), Hahnemann University School of Medicine, Broad and Vine Streets, Philadelphia, PA 19102-1192 (Dr Lebenthal).



Age and sex distribution of children with gallstones. The highest incidence is noted between 16 and 20 years of age. The female predominance was noted only in the second decade. Solid bar indicates males (n = 21); and hatched bar, females (n = 29).

Table 1.—Conditions Associated With Gallstones in 50 Children*

Associated Conditions	No. of Patients
Hemolysis	18
Sickle cell anemia	11
Spherocytosis	3
Autoimmune	2
Thalassemia major	1
Pyruvate kinase deficiency	1
Parenteral nutrition	8
Adolescent pregnancy	7
Ileal resection	4
Obesity†	3
Sepsis	3
Nectrotizing enterocolitis	2
Spinal cord disease	2
Transverse myelitis	1
Spina bifida	1
Other	
Hemobilia	1
Chronic intestinal pseudo-obstruction	1
Chylous ascites	1
Muscular dystrophy	1
Sarcoidosis	1
Systemic lupus erythematosus	1
Hyperlipidemia	1
Cystic fibrosis	1
Hepatitis type B	1
Dysgammaglobulinemia	1
Prolonged ceftriaxone therapy	1
Idiopathic	10

*Children with gallstones could be categorized into four main groups: patients with hemolysis (18), patients with parenteral nutrition (8), adolescent pregnancy (7), and patients with other predisposing factors (7). More than one predisposing factor was present in some patients.

†Obesity is defined as weight divided by height, 95th percentile.

langiogram (for two patients). One patient was diagnosed at laparotomy for a small-bowel obstruction; some patients had more than one diagnostic study.

The relationship between associated factors and age, sex, racial distribution, symptoms, laboratory studies, and therapy is shown in Table 3. The patients with parenteral nutrition were significantly younger than the average age at presentation ($P<.05$), and the pregnant adolescent patients were significantly older ($P<.01$). After exclusion of the adolescent pregnancy group, female predominance was observed only in the miscellaneous group, while the hemolytic, parenteral nutrition, and idiopathic groups had nearly equal sex distributions. Right upper quadrant pain was the chief presenting symptom in all groups except the patients with parenteral nutrition. Jaundice was seen mainly in the hemolytic group. No hemolytic or pregnant adolescent patients were asymptomatic. Leukocytosis was not present in the parenteral nutrition group and was present most commonly in the adolescent pregnancy and hemolytic groups. Elevated serum transaminase levels were seen in all the pregnant patients and half of the hemolytic patients. Cholecystectomy was performed in 36 patients and was the main therapy in all groups except the patients with parenteral nutrition, for whom conservative treatment was preferred.

Complications of gallstones occurred in six patients, including pancreatitis (4 patients), retained duct stone (one patient), and recurrence (one patient). No patient with pancreatitis was found to have a stricture of the Vater's ampulla or other obstruction of the pancreatic duct. The only death occurred in a patient with sickle cell anemia presenting with repeated episodes of biliary colic. The patient's parents refused preoperative transfusions due to religious beliefs.

COMMENT

According to the experience at Children's Hospital of Buffalo and other institutions,[1,5,11] gallstones are currently being diagnosed more frequently in children. This apparent increase in incidence may be attributed to improved diagnostic modalities with their extensive use in abdominal illness, prematurity, and adolescent pregnancy. Alternatively, a true increase in gallstones, which could be confirmed only by a general population–based survey, may be occurring. As more cases of gallstones in children are recognized, there is evidence of associations and clinical manifestations distinct from those cases found in adults.

The female predilection for gallstones in adults was present in our study; however, when the adolescent pregnant patients were excluded, the sexual distribution was equal: 22 females and 21 males. This concurs with other studies.[11-13] The emergence of female predominance starting from puberty supports the hypothesis of a hormonal influence rather than genetic predisposition in the female preponderance seen in adult gallstones.[14]

The mean age of our patients was 12.2 years, which is in accordance with the reports by others[12,13] of a peak incidence between ages 10 and 15 years. Because Children's Hospital of Buffalo is a tertiary neonatal center, our study may include larger numbers of complicated neonates than expected. Eight percent of our cases occurred in patients less than 1 year old, including one case diagnosed in utero by maternal ultrasound

Table 2.—Clinical Presentation in Relation to Age in 50 Children With Gallstones

Symptom	Age, y					
	1	1-5	6-10	11-15	16-20	Total
Right upper quadrant pain	1	0	9	7	15	**32**
Jaundice	0	0	6	6	3	**15**
Vomiting	0	2	2	2	7	**13**
Nonspecific (abdominal pain, nausea, chest pain)	0	3	1	3	6	**13**
Fatty food intolerance	0	0	3	2	1	**6**
Fever	0	0	0	1	0	**1**
Asymptomatic	3	2	0	0	1	**6**

Table 3.—The Relationship Between Predisposing Factors and Age, Race, Sex, Clinical Presentation, Laboratory Studies, and Therapy in 50 Children With Gallstones

	All Patients	Hemolytic	Parenteral Nutrition	Adolescent Pregnancy	Idiopathic	Other
No. of patients	50	18	8	7	10	7
Age, y (mean ± SD)	12.2±6.2	12.6±4.1	6.3±6.9*	18.1±1.6*	10.6±6.7	17.1±2.0
Race						
White	29	7	6	2	9	5
Black	17	11	2	2	1	1
Hispanic	4	0	0	3	0	1
Sex, No. M/F†	21/29	9/9	5/3	0/7	5/5	2/5
Clinical presentation‡						
Right upper quadrant pain	32	11	3	6	7	5
Jaundice	15	12	0	1	1	1
Vomiting	13	0	3	6	1	3
Nonspecific	13	5	2	2	2	2
Fatty food intolerance	6	1	0	1	2	2
Fever	1	1	0	0	0	0
Asymptomatic	6	0	3	0	2	1
Laboratory studies§						
Leukocytosis	16	7	0	4	2	2
Elevated transaminases	22	9	2	7	2	2
Elevated amylase	8	2	0	3	1	2
Therapy						
Conservative	15	3	5	4	3	0
Cholecystectomy	35	15	3	3	7	7

*The patients with parenteral nutrition were significantly younger than the group taken as a whole $P<.05$), while the adolescent pregnancy patients were significantly older than the group as a whole $P<.01$).

†After exclusion of the adolescent pregnancy group, the sex distribution was equal in the patients as a whole.

‡Jaundice was largely confined to the patients with hemolytic disease. Nonspecific abdominal complaints ncluded poorly localized pain, nausea, and chest pain.

§Leukocytosis was defined as white blood cell count >14 × 10^9; elevated transaminase levels defined as alanine aminotransferase >20 U/L, or aspartate aminotransferase >20 U/L; elevated amylase levels defined as >125 U/L.

study. We found that the mean age of the hemolytic patients was 12.6 years, which is compatible with the other reports of congenital hemolytic disease occurring with gallstones in late childhood,[12,13] although the mean age in our study was slightly older. The mean age of the patients with parenteral nutrition was significantly younger than the average age of presentation for all patients in our study ($P<.05$). The idiopathic patients were also younger than the group taken as a whole, but the differences were not statistically significant.

Like other studies,[13] the most common predisposing factor was hemolytic disease, including two patients with autoimmune hemolysis and one patient with pyruvate kinase deficiency. Because adolescent pregnancy is increasing dramatically in the United States,[15] and because pregnant or postpartum teenagers accounted for 14% of the patients in our study, this group merits more consideration from pediatricians. Patients receiving parenteral nutrition are at risk of developing gallstones due to bile stasis,[16] especially those patients not receiving oral supplementation.[17] In addition, patients receiving parenteral nutrition may be further predisposed toward biliary disease by their underlying disease state, such as necrotizing enterocolitis,[18] ileal resection, and ileal disease.[19,20] Determination of the relative importance of each associated factor in these patients is beyond the scope of our study.

Only one patient had cystic fibrosis. This scarcity can be explained by early diagnosis and prompt pancreatic supplementation.[14] Spinal surgery and spinal cord injury have been associated with gallstones in adults[6] and children[7]; our series included one patient with transverse myelitis and one patient with spina bifida. Hemobilia is a rare cause of gallstones in adults[21]; in our series, one patient presented with gallstones 1 year after posttraumatic liver laceration. Finally, only 20% of our patients had no conditions associated with gallstones, which is less than in early reports by Harned and Babbitt[22] and Spahr.[23]

The classic adult presentation of gallstones as biliary colic applies best to children over 15 years of age. The younger patients, especially the patients less than 5 years of age, tended to present with nonspecific symptoms. The ability to localize pain to the right upper quadrant or to relate symptoms to fatty foods depended on the patient's age. Irritability, particularly when occurring after feedings, should suggest the possibility of gallstones, especially in premature infants or infants with a history of parenteral nutrition or necrotizing enterocolitis.

Nearly half of the preschool children were asymptomatic. Diagnosis of gallstones in the asymptomatic young child was often incidental, eg, by ultrasound study performed for recurrent urinary tract infections. The finding of a fever in only one patient underscores the rarity of cholecystitis and cholangitis in children with gallstones.[11]

Jaundice can be related either to common bile duct obstruction or to inflammation in the presence of gallstones confined to the gallbladder. Like other series,[11,24] choledocholithiasis in children was found to be rare, without a single case among our 50 patients. Twelve patients with jaundice had underlying hemolytic disease, and only three patients with jaundice did not have underlying hemolysis, suggesting that biliary obstruction was not the mechanism for the jaundice.

Ultrasonography proved to be a noninvasive, accurate method of diagnosis with no false-positive results in our study. Other methods of diagnosis should be employed when the ultrasonographic findings are not conclusive or when biliary tract anomalies or complications are suspected.

In contrast to adults, in whom cholecystitis, choledocholithiasis, cholangitis, and perforation are the most common complications of gallstones, such complications are rare in children.[11] Pancreatitis was found to be the most common complication, occurring in 8% of the patients, and no patient was documented to have a stricture of the ampulla of vater. One patient with sickle cell anemia died postoperatively. Mortality was attributed to the postoperative complications of the hemolytic disease rather than complications of the gallstones. As in other studies[25] when preoperative transfusions were performed, mortality from cholecystectomy in patients with sickle cell anemia was low. Current medical ethics would favor preoperative transfusion despite parental objection in a patient with sickle cell disease.

The decision between cholecystectomy and conservative management depended on patient age and severity of symptoms; the cause did not have a major impact on the method of treatment. In general, infants and patients with parenteral nutrition were managed more conservatively, and all were managed without specific medical or surgical therapy directed to the stones. Management of asymptomatic gallstones in children is controversial and beyond the scope of our study.

Our results indicate that gallstones in children have a variety of associated factors and presentations. The classic clinical picture, as well as the laboratory confirmation in adults, does not apply to children. Therefore, more attention must be paid to the possibility of gallstones in the evaluation of children with nonspecific abdominal symptoms, especially in children with associated conditions.

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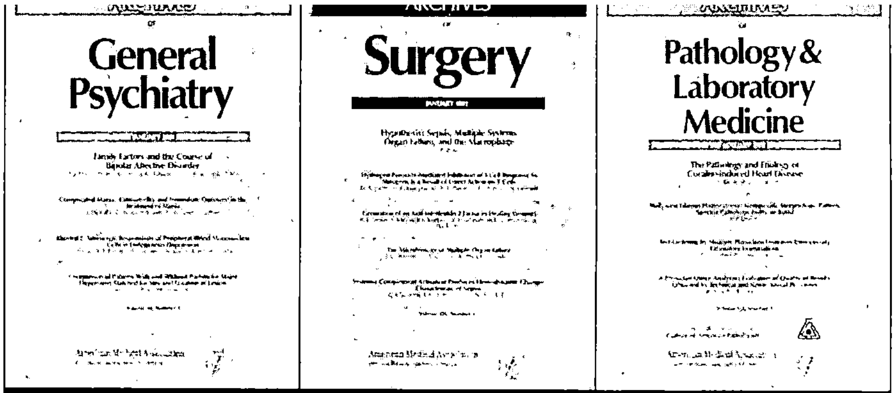

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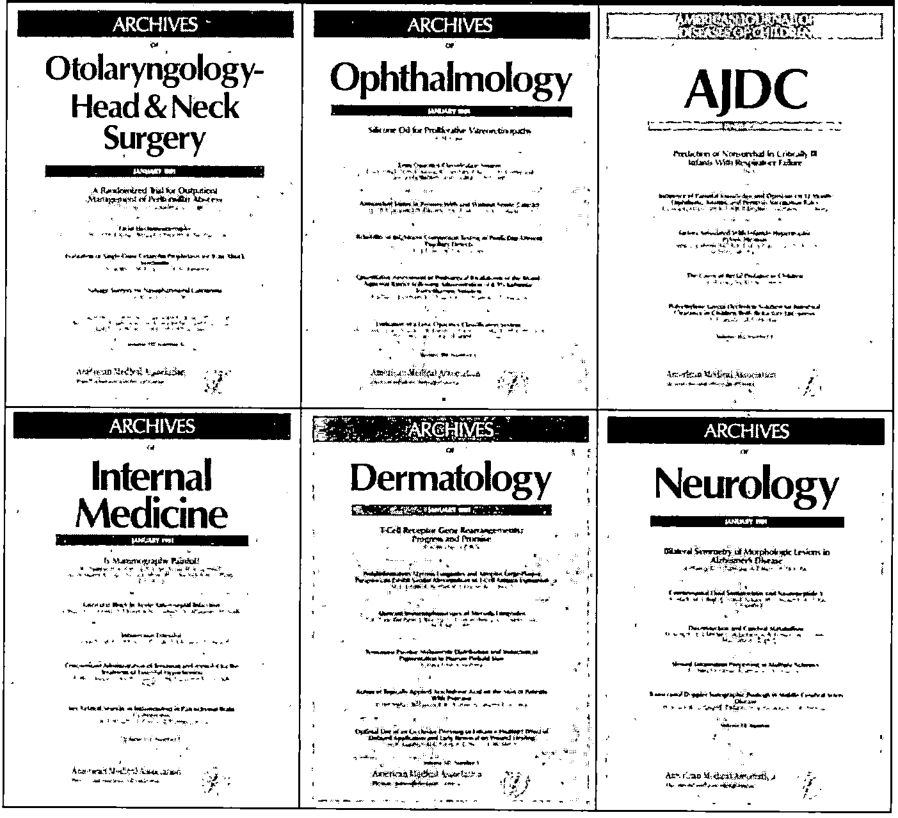

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Step 2.—*Manuscript Format.*—All articles submitted should have the following features:

1. Four copies of the manuscript should be submitted; three are for transmission to referees and one is to be retained in the editorial office. We prefer an original and three copies.

2. Manuscripts should be typed in triple-spaced format on heavy-duty white bond paper, 21.6×27.9 cm (8½×11 in) with 2.5-cm (1-in) margins. *Do not use justified right margins.*

3. Title should be no more than 75 characters.

4. Authors should be limited to six, all of whom have contributed to the study and manuscript preparation, are familiar with its substance, and are able to defend its conclusions.

5. The title page should give full names, degrees, and academic affiliations of all authors, address for request of reprints, and, if the manuscript was presented at a meeting, the organization, place, and exact date on which it was read.

6. Writing style should conform to proper English usage and syntax; consult the *American Medical Association Manual of Style*, available from Williams & Wilkins, 428 E Preston St, Baltimore, MD 21202.

7. Abstract should be limited to 135 words or less.

8. Each table should be typed, with a title, on a separate sheet of paper, with *each line, including headings, double-spaced.* Continuations should be on a second sheet with all headings repeated.

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All photographs in which there is a possibility of patient identification should be accompanied by a signed statement of consent from *both* parents (or guardians). Covering eyes to mask identity is not sufficient.

11. References should be listed in order of their appearance in the text, type double-spaced, and in AMA format. Please follow the exact order of information and punctuation in the examples below. *Note:* List all authors and/or editors up to six; if more than six, list the first three and "et al."

Journal articles: Scott GB, Buck BE, Leterman JG, Bloom FL, Parks WP. Acquired immunodeficiency syndrome in infants. *N Engl J Med.* 1984;310:76-81.

Books: Naeye RL. How and when does antenatal hypoxia damage fetal brains? In: Kubli F, Patel N, Schmidt W, Linderkamp O, eds. *Perinatal Events and Brain Damage in Surviving Children.* New York, NY: Springer Verlag NY Inc; 1988:83-91.

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13. Illustrations and tables from other publications should be suitably acknowledged, with written permission from *publisher* and *author.* Brief acknowledgements to specific contributors directly involved in the content of the manuscript may be placed at the end of the text, before the references. General acknowledgements will be deleted.

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1. *The Pediatric Forum.*—This is the place for comment, criticism, observations, and discussion of "issues of current concern and importance for children's health," in addition to letters that comment on articles in previous issues of *AJDC*. The Editor reserves the right to conduct review of and to edit all submissions. THE READER SHOULD SUBMIT TRIPLE-SPACED COPY CLEARLY MARKED "FOR PUBLICATION" AND SIGNED BY ALL AUTHORS. REFERENCES, IF INCLUDED, SHOULD CONFORM TO THE USUAL AMA FORMAT. Copyright assignment, signed by all authors, must accompany the original submission.

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4. *Sports Medicine.*—PURPOSE: To provide current information related to the medical needs of young athletes, as pertinent to counseling young athletes and their parents regarding sports participation and practices contributing to the health maintenance of the athlete, as well as current concepts in the prevention, diagnosis, and treatment of sports-related illnesses and injuries.

5. *Picture of the Month.*—Submissions should be sent directly to Murray Feingold, MD, National Birth Defects Center, Kennedy Memorial Hospital, 30 Warren St, Brighton, MA 02135, and should conform to the format for original articles in terms of the text, references, and illustrations.

6. *Radiological Case of the Month.*—Submissions should be sent directly to Beverly P. Wood, MD, University of Rochester Medical Center, 601 Elmwood Ave, PO Box 648, Rochester, NY 14642. Submissions should conform to the format for original articles in terms of the text, references, and illustrations.

Author's Checklist

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____ 9. Four sets of illustrations.
____ 10. Four sets of legends for illustrations.
____ 11. Proper consent forms for patient photographs.
____ 12. Permission forms for illustrations previously published elsewhere.

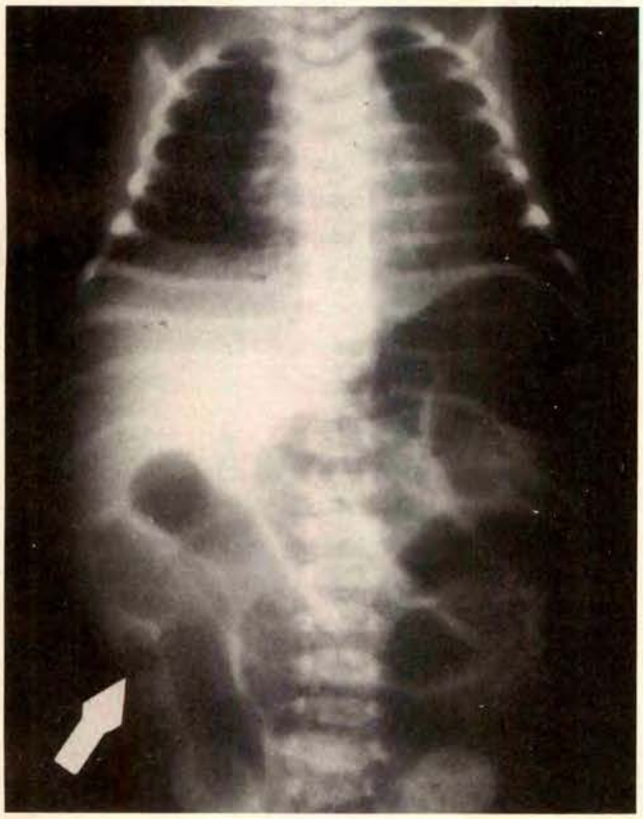
Special Features

Radiological Case of the Month

CPT Michael E. Ruff, MC, USA; MAJ W. Michael Southgate, MC, USA *(Contributors)*;
Beverly P. Wood, MD *(Section Editor)*

A term, 3740-g newborn was admitted for suspected sepsis. Rupture of the membranes had occurred 18 hours prior to delivery and was associated with a maternal temperature of 38.1°C. Apgar scores were eight and nine at 1 and 5 minutes, respectively. A white blood cell count was 14.7×10^9/L, with the following differential cell count: polymorphonuclear cells, 0.16; band cells, 0.31; lymphocytes, 0.21; monocytes, 0.25; and eosinophils, 0.02. An admission blood culture was positive for group B *Streptococcus.* The infant received intravenous ampicillin and gentamicin.

The patient did well until the fourth day after birth when he developed bile-stained emesis. His temperature was 36.8°C. The heart rate was 131 beats per minute. Respirations were 52 per minute. The blood pressure was 77/61 mm Hg. The physical examination revealed a distended abdomen that was tender to palpation and moderately tense. Bowel sounds were hypoactive. The hematocrit was 0.40; the platelet count was 3.78×10^{11}/L. The white blood cell count was 5.6×10^9/L and the differential cell count was as follows: polymorphonuclear cells, 0.23; band cells, 0.17; lymphocytes, 0.41; monocytes 0.08; and atypical cells, 0.10. An abdominal roentgenogram was obtained (Fig 1). A nasogastric tube was placed and a large amount of bilious fluid was drained from the stomach. An upper gastrointestinal tract series with normal results was followed by barium enema examination (Fig 2). The infant was then taken to surgery for an exploratory laparotomy.



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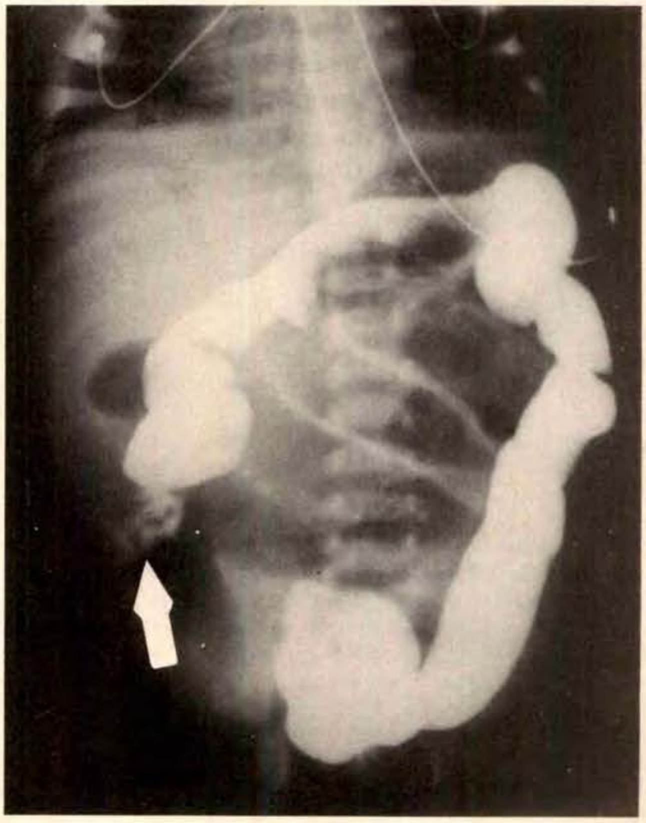

Figure 2.

Accepted for publication January 22, 1990.
Contributed from the Department of Pediatrics, Tripler Army Medical Center, Hawaii.
Reprint requests to the Department of Radiology, Childrens Hospital of Los Angeles, 4650 Sunset Blvd, Los Angeles, CA 90027 (Dr Wood).

Denouement and Discussion

Neonatal Appendicitis With Perforation

Fig 1.—Supine roentgenogram of the abdomen demonstrates multiple long dilated loops of bowel with a fixed collection of apparently extraluminal gas in the right lower quadrant of the abdomen. (arrow).

Fig 2.—Contrast enema demonstrates a colon of normal appearance and caliber distal to the ascending colon. Extravasated barium is present at the cecum (arrow).

Fig 3.—Surgical specimen shows acute suppurative appendicitis with perforation (arrow).

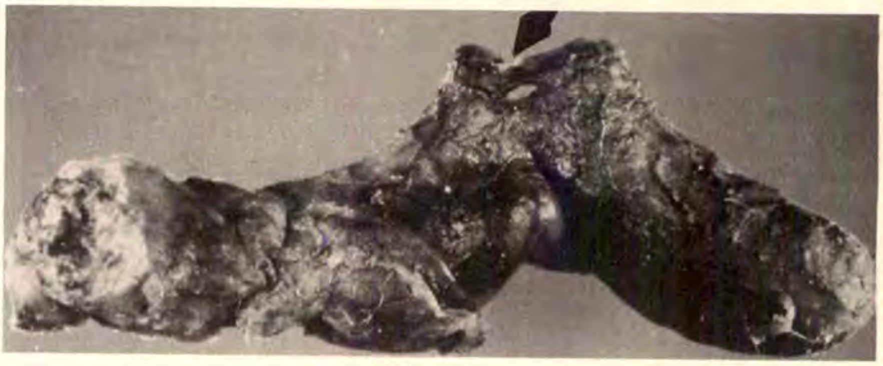

Figure 3.

At laparotomy, there was a large amount of seropurulent fluid in the abdomen. The cecum was indurated and an acutely inflamed appendix, with perforation at its midportion, was present. A culture of the peritoneal fluid was positive for *Klebsiella pneumoniae*. After surgery, the patient received intravenous antibiotics for 7 days. The patient was discharged home on the 18th postoperative day.

Less than 2% of all children treated for appendicitis are younger than 2 years of age.[1,2] Neonatal appendicitis is extremely rare.[3] Diess, as cited by Hemalatha and Spitz,[4] described the first case in 1903. Subsequently, there have been 120 cases reported in the English literature.[5]

The rarity of appendicitis in infancy is primarily ascribed to the conical shape of the infantile appendix, decreasing the likelihood of its obstruction. The appendix assumes its adult vermiform configuration between 1 and 2 years of age.[1] Other factors cited include the soft diet of neonates and the decreased incidence of viral-induced appendiceal lymphoid hyperplasia.[6]

Although earlier diagnosis of the acute abdomen in neonates and improved postoperative care have contributed to increased survival, there are several reasons why neonatal appendicitis continues to have a high mortality.[3] First, there is a high incidence of perforation. This is attributed to the thin wall of the neonatal appendix as well as the fact that the cecum does not distend easily in infancy and therefore cannot help decompress the appendix.[5] Perforated neonatal appendicitis occurs with increased incidence in association with obstructive lesions, such as Hirschsprung's disease.[7,8] The second factor that contributes to the high mortality of patients with this disease is the very limited ability of the neonate to combat the complications of appendiceal perforation. This is due to an immature immune system and an underdeveloped omentum, which is short and thin and has little capacity to wall off infection.[9]

The clinical presentations of neonatal appendicitis are abdominal distention (80%) and vomiting (60%).[3] Other less consistent findings are irritability, anorexia, fever, cellulitis, abdominal tenderness, hypoperistalsis, and leukocytosis.[3] In addition, 27 (29%) of the 94 patients described by Srouji and Buck[10] presented with a hernial mass. This manifestation of the disease process leads to earlier recognition and surgical intervention. Isolation of the inflammatory process within the hernial sac contributes to decreased mortality.[10]

Unique to this case is the history of group B streptococcal sepsis. The possibility of an antecedent bacteremia as a pathologic agent in neonatal appendicitis has not been previously reported to our knowledge, and we postulate that it was coincidental in this case.

In the roentgenographic evaluation of a neonate with suspected appendicitis, an acute abdominal series is useful in establishing the diagnosis but is not specific.[11] A contrast enema examination may be of value by demonstrating nonfilling of the appendix or, as in our patient, revealing extravasation of contrast near the cecum.[3]

The differential diagnosis of neonatal appendicitis includes sepsis, necrotizing enterocolitis, pancreatitis, intestinal atresia, meconium ileus, and Hirschsprung's disease.

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Picture of the Month

Jeffrey L. Loughead, MD; Francis Mimouni, MD; Sue Schilling, RN (*Contributors*);
Murray Feingold, MD (*Section Editor*)

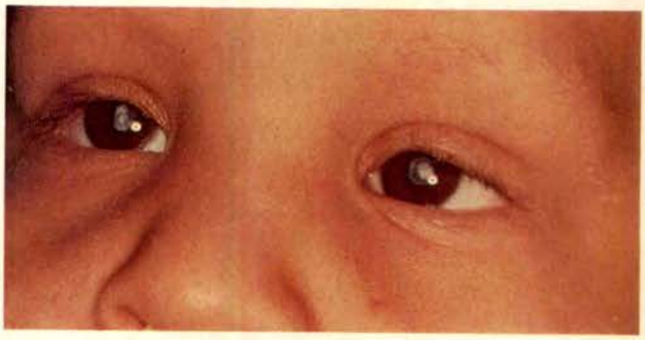
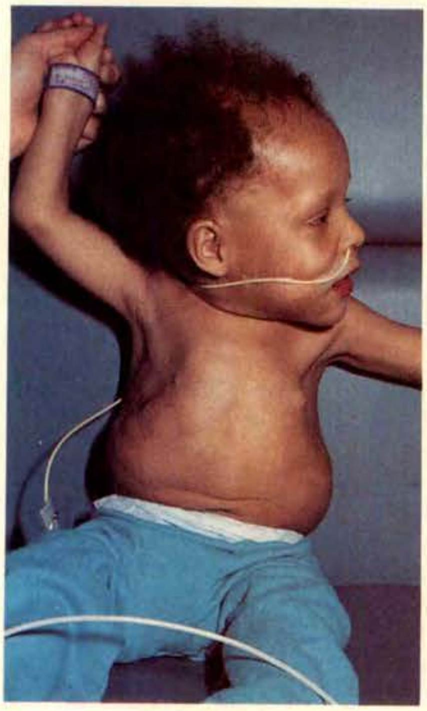


Figure 1.



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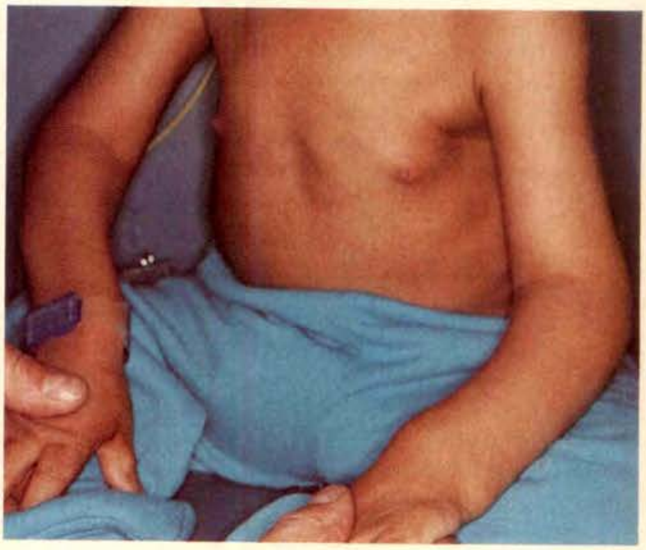

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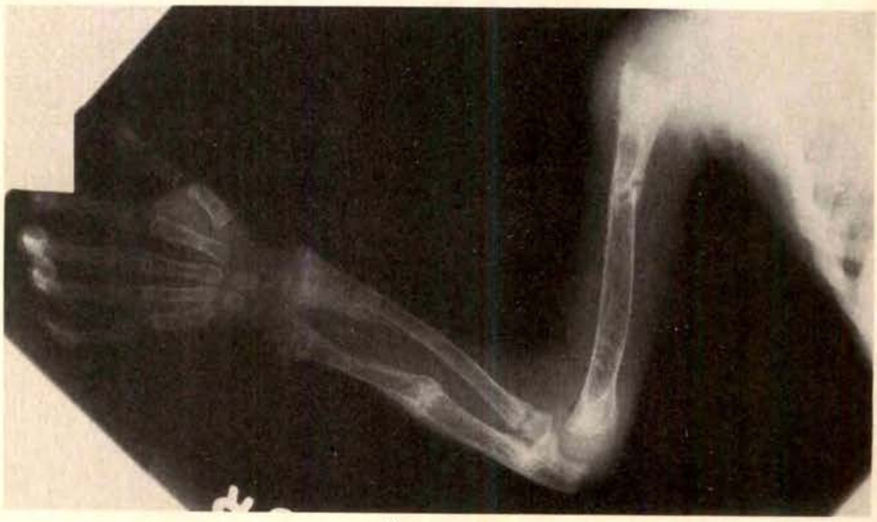

Figure 4.

Accepted for publication April 12, 1990.

From the Division of Neonatology, Department of Pediatrics, University of Cincinnati, Ohio.

Reprint requests to National Birth Defects Center, Franciscan Children's Hospital, 30 Warren St, Brighton, MA 02135 (Dr Feingold).

Denouement and Discussion

Lowe's Syndrome

Fig 1.—Centrally located, bilateral cataracts.

Fig 2.—Sparse hair, bell-shaped chest with rachitic rosary, thin limbs with decreased muscle mass, and signs of hypotonia.

Fig 3.—Marked bowing of forearms and prominent metaphyseal enlargement of left wrist.

Fig 4.—Roentgenographic examination of the right arm showing markedly poor calcification of the bones with splaying and cupping of the metaphyses of the radius, ulna, and humerus. Also present are multiple fractures in various stages of healing.

Lowe's syndrome, or oculocerebrorenal syndrome, is an X-linked hereditary disease characterized by congenital ocular disease, renal tubular dysfunction, hypotonia, moderate to severe bone disease, and mental retardation. It is present in all races, with a predominance in those with Caucasian and Asian ancestries.

The disease has three identifiable stages. The first, during the newborn period, is characterized by ocular pathologic features. Nearly all affected individuals have congenital, centrally located cataracts that are frequently associated with glaucoma and a miotic pupil. Asymptomatic aminoaciduria is usually found during this stage and a generalized aminoaciduria develops by age 1 year. This is often accompanied by varying degrees of proteinuria.

The second stage occurs during early childhood and is dominated by metabolic acidosis. The underlying basis for the disturbances is not known, but central to many of the symptoms appears to be a renal tubular dysfunction that results in urinary loss of bicarbonate, glucose, calcium, phosphorus, and protein. As a result of this serum metabolic acidosis and losses of calcium and phosphorus, secondary hyperparathyroidism occurs. Severe rickets and demineralization may develop leading to frequent fractures, pain, and delay or loss of normal motor physical development. The severe hypophosphatemia may lead to weakness and lethargy.

In the third stage, the metabolic disturbances of early childhood may continue or become progressively less severe, and have even been reported to resolve entirely. The prominent manifestations of this period are largely related to the sequelae of the previous two stages. This includes blindness from a combination of glaucoma and cataracts and orthopedic disabilities associated with the severe bone disease. Mental retardation has been described as moderate to severe and is of unknown origins. Computed tomography shows confluent irregular lucencies in the cerebral white matter, especially in the periventricular areas, and magnetic resonance imaging reveals patchy areas of white-matter demyelination. Electroencephalograms often demonstrate nonspecific abnormalities; however, some may show overt seizure activity. Auditory acuity is generally normal.

Genetics

The etiologic and biochemical basis of this syndrome is yet unknown. The inheritance pattern appears to be X-linked recessive and recent gene mapping, using tightly linked flanking markers, has placed the probable gene site at Xq24-26. The carrier state is identifiable through family history, ophthalmic examination, and genetic mapping. Slit-lamp examination of carriers has revealed increased numbers of punctate lenticular opacifications as early as the second decade of life. These lenticular opacifications appear to be the only clinical manifestation in the carrier. Prenatal diagnosis using flanking gene markers is now theoretically possible with a high degree of accuracy.

Treatment

Therapy consists mainly of supportive care. The renal tubular acidosis and rickets respond well to a combination of sodium-potassium citrate and phosphorus replacement. Vitamin D supplement therapy may be of benefit. Close attention to general nutrition and ophthalmic disease are important to enhance development. Despite treatment, the prognosis for mental development is guarded and death often occurs in the second decade of life. Genetic counseling should be provided.

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Our special appreciation is extended to each person on this list for his or her efforts on behalf of our readers, authors, and editorial staff.

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References: 1. Fomon SJ, Ziegler EE, Nelson SE, et al: Sweetness of diet and food consumption by infants. *Proc Soc Exp Biol Med* 173:190-193, 1983. 2. Lebenthal E, Leung Y-K: The impact of development of the gut on infant nutrition. *Pediatr Ann* 16:211-222, 1987. 3. Data on file, Wyeth-Ayerst Laboratories.

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DISEASES OF CHILDREN

12/92

217

AJDC

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MARCH 1991

Practice Management Training for Pediatric Residents

J. P. Piatt, D. L. Bartley, A. D. Jacobson, M. E. Rimsza

Standardized Percentile Curves of Body-Mass Index for Children and Adolescents

L. D. Hammer, H. C. Kraemer, D. M. Wilson,
P. L. Ritter, S. M. Dornbusch

Improved Speed and Accuracy of Calculations With a Programmable Calculator in Pediatric Emergency Scenarios

M. Melzer-Lange, D. Wyatt, C. Walsh-Kelly, D. Smith,
M. A. Hegenbarth, C. S. L. Eisenberg

Physicians, Formula Companies, and Advertising: A Historical Perspective

F. R. Greer, R. D. Apple

Photographing the Physically Abused Child: Principles and Practice

L. R. Ricci

Cortical Resection for Children With Epilepsy: Perspectives in Pediatrics

E. Wyllie

Volume 145, Number 3

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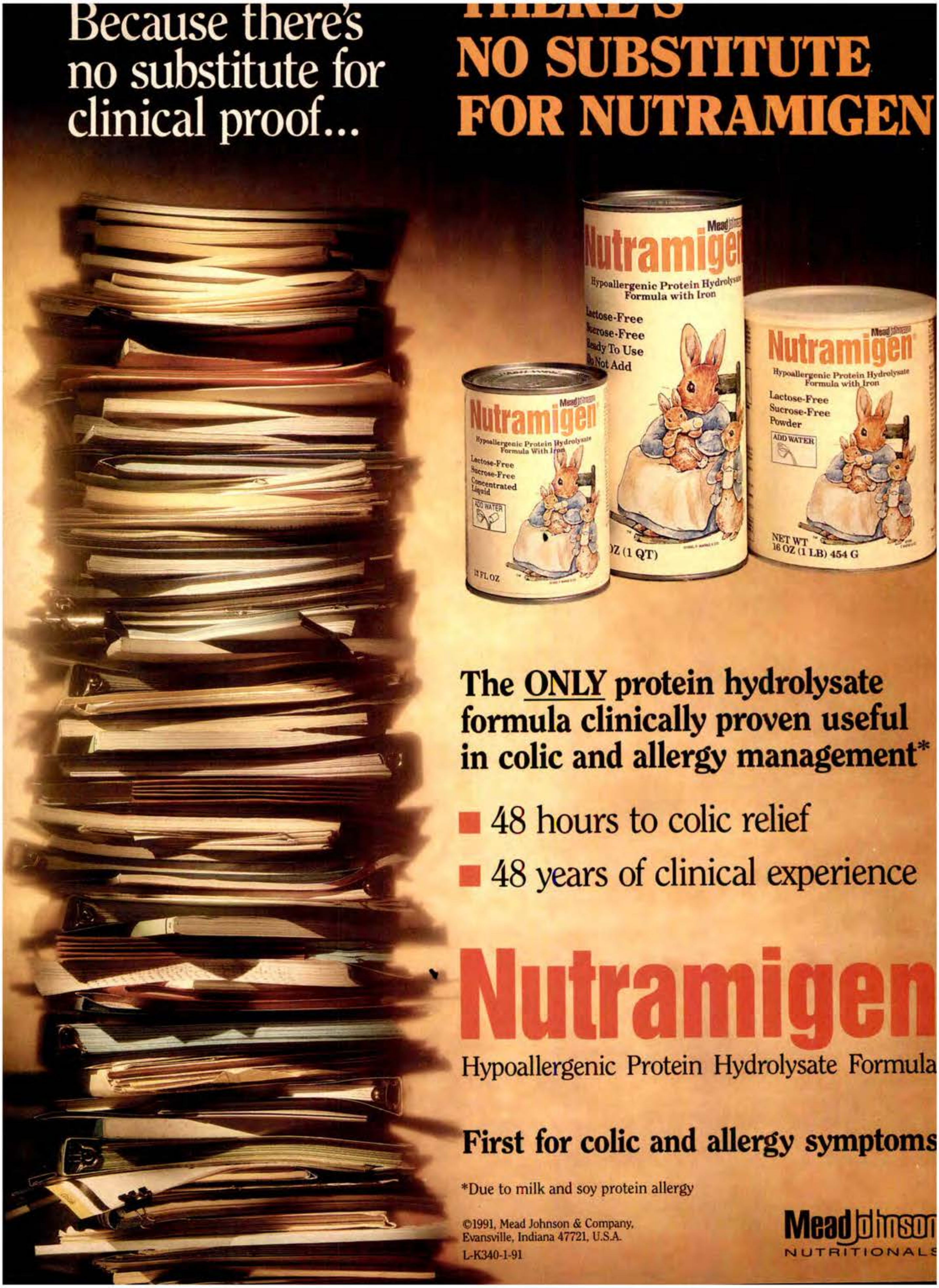

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AMERICAN JOURNAL OF
DISEASES OF CHILDREN

AJDC

Vol 145 **No. 3** **MARCH 1991**

THE PEDIATRIC FORUM

1991 Annual Meeting 249

More on the *P* Value 249
David M. Coulter, MD, Salt Lake City, Utah

In Reply 249
George W. Brown, MD, Los Lunas, NM

Multiple Comparisons and *P* Values 250
Thomas B. Newman, MD, MPH;
Warren S. Browner, MD, MPH, San Francisco, Calif

***P* Values** 250
Ted Byrt, Parkville, Australia

Clavicular Fractures in Neonates: Frequency vs Significance 251
Michael J. O'Halloran, Eau Claire, Wis

In Reply 251
Paul R. Joseph, MD, Mineola, NY

Clavicular Fractures in Neonates 251
Gloria Carter, RN, PNP; J. W. Park, MD, Odessa, Tex

In Reply 252
Paul R. Joseph, MD; Warren Rosenfeld, MD, Mineola, NY

What About Gay Teenagers? 252
Charles R. Fikar, MD; Mary Koslap-Petraco, BSN, RN, Deer Park, NY

EDITORIALS

Pediatric Legal Medicine: A New Venture 255
Peggy C. Ferry, MD, Tucson, Ariz

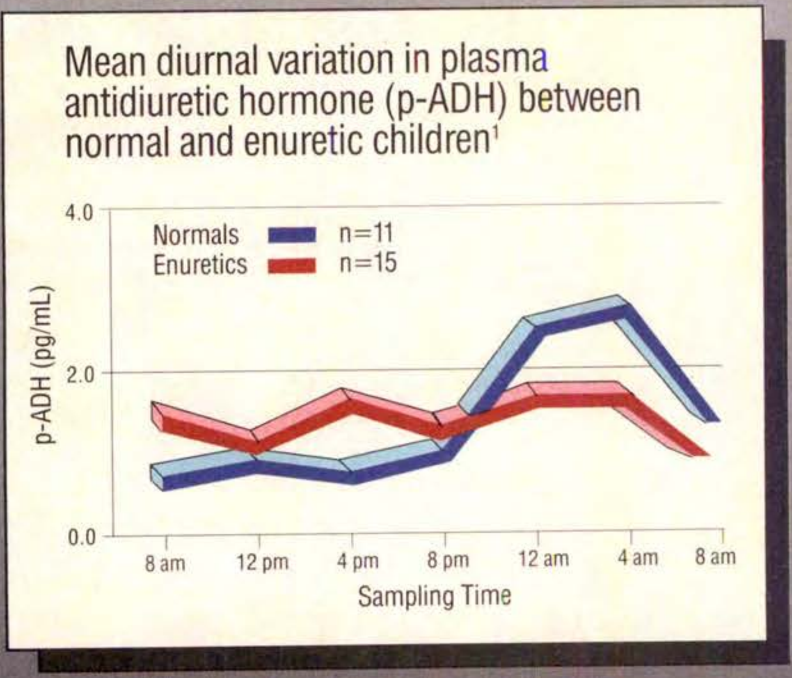
Pediatric Perspectives: Vistas and Vantage Points 256
Alan D. Bedrick, MD, Tucson, Ariz

THE EDITORIAL BOARD SPEAKS

Your Child's Best Friend: TV or Not TV 257
E. Richard Stiehm, MD, Philadelphia, Pa

Continued on page 245.

Landmark study concludes: Enuretic children may lack diurnal rhythm of ADH common in non-enuretic children[1]



Mean diurnal variation in plasma antidiuretic hormone (p-ADH) between normal and enuretic children[1]

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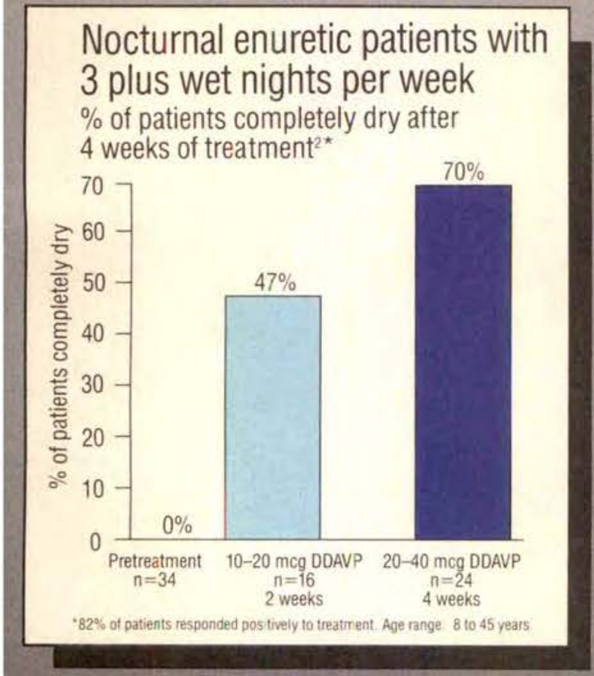

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Primary Nocturnal Enuresis: If changes in the nasal mucosa have occurred, unreliable absorption may result. DDAVP intranasal solution should be discontinued until the nasal problems resolve.
Information for Patients: Patients should be informed that the bottle accurately delivers 50 doses of 10 mcg each. Any solution remaining after 50 doses should be discarded since the amount delivered thereafter may be substantially less than 10 mcg of drug. No attempt should be made to transfer remaining solution to another bottle. Patients should be instructed to read accompanying directions on use of the spray pump carefully before use.
Laboratory Tests: For the healthy patient with primary nocturnal enuresis, serum electrolytes should be checked at least once if therapy is continued beyond 7 days.
DRUG INTERACTIONS: Although the pressor activity of DDAVP is very low compared to the antidiuretic activity, use of large doses of DDAVP with other pressor agents should only be done with careful patient monitoring.
CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY: Teratology studies in rats have shown no abnormalities. No further information is available.
PREGNANCY—CATEGORY B: Reproduction studies performed in rats and rabbits with doses up to 12.5 times the human intranasal dose (i.e. about 125 times the total adult human dose given systemically) have revealed no evidence of harm to the fetus due to desmopressin acetate. There are several publications of management of diabetes insipidus in pregnant women with no harm to the fetus reported; however, no controlled studies in pregnant women have been carried out. Published reports stress that, as opposed to preparations containing the natural hormones, DDAVP (desmopressin acetate) in antidiuretic doses has no uterotonic action, but the physician will have to weigh possible therapeutic advantages against possible dangers in each individual case.
NURSING MOTHERS: There have been no controlled studies in nursing mothers. A single study in a postpartum woman demonstrated a marked change in plasma, but little if any change in assayable DDAVP in breast milk following an intranasal dose of 10 mcg.
PEDIATRIC USE: Primary Nocturnal Enuresis: DDAVP has been used in childhood nocturnal enuresis. Short-term (4-8 weeks) DDAVP administration has been shown to be safe and modestly effective in children aged 6 years or older with severe childhood nocturnal enuresis. Adequately controlled studies with intranasal DDAVP in primary nocturnal enuresis have not been conducted beyond 4-8 weeks. The dose should be individually adjusted to achieve the best results.
There are reports of an occasional change in response with time, usually greater than 6 months. Some patients may show a decreased responsiveness, others a shortened duration of effect. There is no evidence this effect is due to the development of binding antibodies but may be due to a local inactivation of the peptide.
ADVERSE REACTIONS: Infrequently, high dosages have produced transient headache and nausea. Nasal congestion, rhinitis and flushing have also been reported occasionally along with mild abdominal cramps. These symptoms disappeared with reduction in dosage. Nosebleed, sore throat, cough and upper respiratory infections have also been reported.
The following table lists the percent of patients having adverse experiences without regard to relationship to study drug from the pooled pivotal study data for nocturnal enuresis.

ADVERSE REACTION	**PLACEBO (N=59)** %	**DDAVP 20 mcg (N=60)** %	**DDAVP 40 mcg (N=61)** %
BODY AS A WHOLE			
Abdominal Pain	0	2	2
Asthenia	0	0	2
Chills	0	0	2
Headache	0	2	5
Throat Pain	2	0	0
NERVOUS SYSTEM			
Depression	2	0	0
Dizziness	0	0	3
RESPIRATORY SYSTEM			
Epistaxis	2	3	0
Nostril Pain	0	2	0
Respiratory Infection	2	0	0
Rhinitis	2	8	3
CARDIOVASCULAR SYSTEM			
Vasodilation	2	0	0
DIGESTIVE SYSTEM			
Gastrointestinal Disorder	0	2	0
Nausea	0	0	2
SKIN & APPENDAGES			
Leg Rash	2	0	0
Rash	2	0	0
SPECIAL SENSES			
Conjunctivitis	0	2	0
Edema Eyes	0	2	0
Lachrymation Disorder	0	0	2

OVERDOSAGE: See adverse reactions above. In case of overdosage, the dose should be reduced, frequency of administration decreased, or the drug withdrawn according to the severity of the condition. There is no known specific antidote for DDAVP.
An oral LD_{50} has not been established. An intravenous dose of 2 mg/kg in mice demonstrated no effect.
HOW SUPPLIED: A 5 mL bottle with spray pump delivering 50 doses of 10 mcg (NDC 0075-2450-02). Keep refrigerated at 36°-46°F (2°-8°C). When traveling, product will maintain stability for up to 3 weeks when stored at room temperature, 72°F (22°C).
See product circular for full prescribing information. Rev. 6/89

1. Rittig S, Knudsen UB, Nørgaard JP, et al: Abnormal diurnal rhythm of plasma vasopressin and urinary output in patients with enuresis. *Am J Physiol* 1989;25(4):F664-F671. 2. Rittig S, Knudsen UB, Sørensen S, et al: Long-term double-blind cross-over study of desmopressin intranasal spray in the management of nocturnal enuresis. In: Meadow SR, ed. *Desmopressin in Nocturnal Enuresis: Proceedings of an International Symposium.* England: Horus Medical Publications; 1988:43-55. 3. Dimson SB: DDAVP and urine osmolality in refractory enuresis. *Arch Dis Child* 1986;61:1104-1107. 4. Data on file, Rhône-Poulenc Rorer Pharmaceuticals Inc. 5. Richardson DW, Robinson AG: Diagnosis and treatment: Drugs five years later: Desmopressin. *Ann Intern Med* 1985;103:228-239.

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INDEX TO ADVERTISERS

B. F. Ascher & Company, Inc .... Cover 3

Burroughs Wellcome Company 248A-B, 274

Children's Hospital of the King's Daughters 336

ICN Pharmaceuticals, Inc 256A-D

Lederle Laboratories 253-254

McNeil Consumer Products Company 246, 320A-B, 335-336

Mead Johnson Nutritional Division .... Cover 2, 337

Merck Sharp & Dohme
Division of Merck & Co., Inc. 343-344

Nemours Children's Clinic 336

Partnership For A Drug-Free America 334

Rorer Pharmaceuticals 242-244

Wyeth-Ayerst Laboratories .... Cover 4

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AMERICAN JOURNAL OF DISEASES OF CHILDREN

ARTICLES

Standardized Percentile Curves of Body-Mass Index for Children and Adolescents 259
Lawrence D. Hammer, MD; Helena C. Kraemer, PhD; Darrell M. Wilson, MD; Philip L. Ritter, PhD; Sanford M. Dornbusch, PhD, Palo Alto, Calif

Improved Speed and Accuracy of Calculations With a Programmable Calculator in Pediatric Emergency Scenarios 264
Marlene Melzer-Lange, MD; David Wyatt, MD; Christine Walsh-Kelly, MD; Douglas Smith, MD; Mary A. Hegenbarth, MD; Carl S. L. Eisenberg, MD, Milwaukee, Wis

Psychosocial Predictors of Maternal and Infant Health Among Adolescent Mothers 267
W. Thomas Boyce, MD; Elizabeth A. Chesterman; Marilyn A. Winkleby, PhD, San Francisco, Calif

Physicians, Formula Companies, and Advertising: A Historical Perspective 282
Frank R. Greer, MD, Rima D. Apple, PhD, Madison, Wis

Ventriculitis in Newborns With Myelomeningocele 287
Edward B. Charney, MD; Jeanne B. Melchionni, RN; Donna L. Antonucci, MD, Philadelphia, Pa

Stimulant Medication and Attention Deficit Disorder: The Child's Perspective 291
Jennifer Bowen, MBBS; Terence Fenton, PhD; Leonard Rappaport, MD, Boston, Mass

Capillary Refilling (Skin Turgor) in the Assessment of Dehydration 296
Jose M. Saavedra, MD; Glenn D. Harris, MD; Song Li, MD; Laurence Finberg, MD, Brooklyn, NY

Neonatal Hepatitis and Extrahepatic Biliary Atresia Associated With Cytomegalovirus Infection in Twins 302
Michael H. Hart, MD; Stuart S. Kaufman, MD; Jon A. Vanderhoof, MD; Rodney S. Markin, MD; Robert Kruger, MD; Dean L. Antonson, MD, Omaha, Neb

Breast-feeding Initiation in a Triethnic Population 306
David E. Bee, PhD; Tom Baranowski, PhD; David K. Rassin, PhD; C. Joan Richardson, MD, Augusta, Ga; William Mikrut, MS, Galveston, Tex

Esophageal Motility in Children With Hirschsprung's Disease 310
Annamaria Staiano, MD, Naples, Italy; Enrico Corazziari, MD, Rome, Italy; Maria Rosaria Andreotti, MD, Naples, Italy; Ray E. Clouse, MD, St Louis, Mo

Adipsic Hypernatremia in Two Sisters 321
Giorgio Radetti, MD; Francesco Rizza, MD; Giuseppe Mengarda, MD; Klaus Pittschieler, MD, Bolzano, Italy

Continued on page 247.

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AMERICAN JOURNAL OF DISEASES OF CHILDREN

Anergy in Pediatric Head Trauma Patients 326
Nevin W. Wilson, MD, La Jolla, Calif; Ann Gooding, MD; Bradley Peterson, MD; John F. Bastian, MD, San Diego, Calif

Endocrine Function in Children With Human Immunodeficiency Virus Infection 330
Lisa J. Schwartz, DO, Bronx, NY; Yolaine St Louis, MD, Brooklyn, NY; Richard Wu, MD; Andrew Wiznia, MD; Arye Rubinstein, MD; Paul Saenger, MD, Bronx, NY

LEGAL MEDICINE

Photographing the Physically Abused Child: Principles and Practice 275
Lawrence R. Ricci, MD, Waterville, Me

EDUCATIONAL INTERVENTION

Practice Management Training for Pediatric Residents 299
Janice P. Piatt, MD; Douglas L. Bartley, MD; Albert D. Jacobson, MD; Mary E. Rimsza, MD, Phoenix, Ariz

PERSPECTIVES

Cortical Resection for Children With Epilepsy: Perspectives in Pediatrics 314
Elaine Wyllie, MD, Cleveland, Ohio

SPECIAL FEATURES

Radiological Case of the Month 339
Michele K. Holloway, MD; Suman Wason, MD, MBA; J. Paul Willging, MD; Charles M. Myer III, MD, Cincinnati, Ohio; Beverly P. Wood, MD, Los Angeles, Calif

Picture of the Month 341
Diane E. Friedman, MEd; Richard J. Pines, DO; Matthew Shelley, MD; Pamela Fisher, MD; G. Michael Silberbach, MD, Portland, Ore; Murray Feingold, MD, Brighton, Mass

REGULAR DEPARTMENTS

Index to Advertisers 244

Instructions for Authors 248

Classified Advertising 345

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7. Abstract should be limited to 135 words or less.

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Journal articles: Scott GB, Buck BE, Leterman JG, Bloom FL, Parks WP. Acquired immunodeficiency syndrome in infants. N Engl J Med. 1984;310:76-81.

Books: Naeye RL. How and when does antenatal hypoxia damage fetal brains? In: Kubli F, Patel N, Schmidt W, Linderkamp O, eds. *Perinatal Events and Brain Damage in Surviving Children.* New York, NY: Springer Verlag NY Inc; 1988:83-91.

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Authors are responsible for the accuracy of the references.

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Step 3.—*Special Departments.*—Criteria for several special departments are given below.

1. *The Pediatric Forum.*— This is the place for comment, criticism, observations, and discussion of "issues of current concern and importance for children's health," in addition to letters that comment on articles in previous issues of *AJDC.* The Editor reserves the right to conduct review of and to edit all submissions. THE READER SHOULD SUBMIT TRIPLE-SPACED COPY CLEARLY MARKED 'FOR PUBLICATION' AND SIGNED BY ALL AUTHORS. REFERENCES, IF INCLUDED, SHOULD CONFORM TO THE USUAL AMA FORMAT. Copyright assignment, signed by all authors, must accompany the original submission.

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5. *Picture of the Month.*—Submissions should be sent directly to Murray Feingold, MD, National Birth Defects Center, Kennedy Memorial Hospital, 30 Warren St, Brighton, MA 02135, and should conform to the format for original articles in terms of the text, references and illustrations.

6. *Radiological Case of the Month.*—Submissions should be sent directly to Beverly P. Wood, MD, University of Rochester Medical Center, 601 Elmwood Ave, PO Box 648, Rochester, NY 14642. Submissions should conform to the format for original articles in terms of the text, references, and illustrations.

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1991 Annual Meeting

The annual meeting of The American Pediatric Society, The Society for Pediatric Research, and The Ambulatory Pediatric Association will be held April 29 through May 2, 1991, at the New Orleans (La) Hilton and Rivergate Convention Center. For further information, contact the APS/SPR Association Headquarters, 2650 Yale Blvd SE, Suite 104, Albuquerque, NM 87106; (505) 764-9099; FAX (505) 842-8227; or the Ambulatory Pediatric Association, 6728 Old McLean Village, McLean, VA 22101; (703) 556-9222.

More on the *P Value*

Sir.—Brown's discussion[1] on the P value continues his elegant series of lucid dissertations on medical statistics. A brief clarification is needed, however, concerning the issue of multiple statistical tests and the risk of type I error. Such corrections to compensate for multiple tests on the same data set are important during "data dredging" expeditions, explorations of a data set in search of statistical differences that were not anticipated by the original study design or hypothesis. As Brown points out, there is one chance in 20 that any such comparison will be significant at the $P = .05$ level. The corrected P values also protect against the type I error, which can occur when "in examining the treatment means we notice a combination that we did not intend to test but which seems unexpectedly large."[2]

In contrast to the data dredger is the investigator who designs a prospective study to test specific hypotheses that involve comparisons of several end points. As long as the comparisons made were planned in advance and address variables that might reasonably be expected to change with the intervention under study, it is probably inappropriate to employ corrections of P values. For example, a study of the effects of a pressor drug would test the hypothesis that treatment would improve systemic blood pressure, cardiac output, and left ventricular contractility. It would be appropriate to define the significance of these changes as $P = .05$. Applying the Bonferroni correction to each would needlessly increase the possibility of missing real differences. However, if this investigator later decides to review the data to compare the incidence of acne, borborygmi, and divorce in the treated and control groups, outcomes not anticipated in the study design and unsupported by a specific hypothesis prior to examining the data, correction of these P values *would* be appropriate.

Although it is difficult to make hard and fast rules that apply in all situations, Armitage's conclusions[3] seem reasonable. Multiple comparison methods "are appropriate only when means are being compared in an exploratory way to see what might 'turn up.' When comparisons are made which flow naturally from the plan of the experiment or survey, the usual *t* test is appropriate."

The carefully crafted prospective study is a refined instrument to test hypotheses. Arbitrary application of statistical correction needlessly blunts this instrument. Data dredging is a clumsy but effective way to generate hypotheses. Conclusions derived from these fishing trips deserve correction and appropriate skepticism.

David M. Coulter, MD
The University of Utah
Department of Pediatrics
Eighth Avenue and C Street
Salt Lake City, UT 84143

1. Brown GW. *P* values. *AJDC.* 1990;144:493-495.
2. Snedecor GW, Cochran WG. *Statistical Methods.* 7th ed. Ames, Iowa: Iowa State University Press; 1980:232.
3. Armitage P. *Statistical Methods in Medical Research.* Boston, Mass: Blackwell Scientific Publications Inc; 1971:207.

In Reply.—The essay on P values was meant to alert readers to possible adverse *numeric* consequences of repeated, mindless, automatic grinding out of statistical tests. (This kind of unplanned data dredging might employ an automaton named Robostat.) I also wanted to point out the usefulness of the binomial expansion $[(p + q)^n = 1.0]$ in some ordinary biomedical situations.

Dr Coulter raises an interesting technical issue in *hypothesis testing.* Hypothesis formation and testing are somewhat different, and much more complex, subjects than those addressed in the essay on P values. Research hypotheses involve elements that are much more "scientific" than mere probability phenomena. Researchers incorporate many elements into their hypotheses, elements such as prior experience, extrinsic knowledge, biologic plausibility, subjective judgments, and so on.

For example, the essay on P values omitted discussion of one-tailed vs two-tailed statistical tests. The decision whether to use a one-tailed or a two-tailed test depends on the judgment of the researcher; the algebra is incidental.

The letter mentions compari sons "planned in advance" that address variables that ". . . might *reasonably* be expected to change . . ." (emphasis added). Reasonableness is a function of hypothesis formation, not of algebra; the numbers are neutral.

It is not universally agreed among biostatistical authorities that no adjustment of separate P values is needed if the hypotheses are stated in advance of evaluating the observations. For example, Fleiss[1] discusses

This department of *AJDC* is reserved for comment, criticism, observation, and discussion of "issues of current concern and importance for children's health." The Editor encourages our readers to express themselves on a variety of topics and issues. Further, we encourage the submission of unique and brief clinical and scientific observations that do not fulfill the criteria for original articles.

the Bonferroni adjustment in comparisons ". . . specified before the data are examined. . . ."

There is general agreement that statistical tests are more credible when used to evaluate hypotheses stated prior to examing the data. A pioneer in pediatric research, William Silverman, MD, tells of the rifleman who displays his bullet lodged in the center of a bull's eye drawn on the side of a barn. Was the target there before the shot was fired, or was the shot fired, and then the target drawn around the bullet?

George W. Brown, MD
PO Box 1269
Los Lunas, NM 87031

1. Fleiss JL. *The Design and Analysis of Clinical Experiments.* New York, NY: John Wiley & Sons Inc; 1986:104.

Multiple Comparisons and *P* Values

Sir.—We would like to comment on the multiple-comparisons problem posed by Brown[1] in his recent contribution about *P* values. The problem is: why should an investigator who wishes to compare treatments A and B be required to demonstrate a greater level of statistical significance if he or she studies treatment C at the same time? On the one hand, there is an apparent need to protect against the increased risk of a type I error associated with making multiple comparisons. On the other hand, it is counterintuitive that the conclusion for the comparison between A and B differs depending on whether the investigator had the resources to study treatment C at the same time.

Brown suggested leaving this enigma to experts in probability. While we do not claim such expertise, we have offered an explanation of this apparent contradiction that some of our colleagues have found helpful.[2] The multiple-comparisons problem in statistics has a ready analogy in clinical medicine: the problem of interpreting a serum chemistry panel. It is true that a chemistry panel with 20 independent tests has a probability of about 64% of including at least one value outside of the "normal" (95%) range in a normal person. What a clinician usually needs to know, however, is not the probability of finding an abnormality in a normal person, but the probability that a person is abnormal, given an abnormal test result. That probability does not depend on how many other tests were done at the same time, but on the other characteristics of the patient, which determine his or her "prior probability" of having a particular disease.

In a patient with oliguria, for example, an elevated serum creatinine level is just as likely to indicate renal disease if it was ordered as part of a 20-test panel, as if it was ordered as a single test. The reason that so many laboratory abnormalities that turn up on chemistry panels do not represent real disease is that few of the tests were ordered because of a clinical suspicion of abnormality. In general, when we order a panel of 20 tests, we may be fishing for abnormalities we have no reason to suspect, whereas when we perform just one test on a patient, it is because we are suspicious that results from that particular test will be abnormal.

The same general principle holds for multiple statistical comparisons: often, the more comparisons investigators make, the less they know about what they are looking for.[3] The problem is not with the multiple comparisons themselves, but with the hypotheses being tested, which start out less likely to be true (low prior probability). Even with a statistically significant result, the evidence often remains unconvincing. Thus, when interpreting *P* values, as when evaluating patients, any "significant" results must be interpreted in the context of other evidence.

Thomas B. Newman, MD, MPH
Division of General Pediatrics
Department of Pediatrics
School of Medicine
University of California
74 New Montgomery St,
Suite 600
San Francisco, CA 94105

Warren S. Browner, MD, MPH
Division of General
Internal Medicine
Department of Medicine
School of Medicine
University of California
74 New Montgomery St,
Suite 600
San Francisco, CA 94105

1. Brown GW. *P* values. *AJDC.* 1990;144:493-495.
2. Browner WS, Newman TB. Are all significant *P* values created equal?: the analogy between diagnostic tests and clinical research. *JAMA.* 1987;257:2459-2463.
3. Rothman KJ. No adjustments are needed for multiple comparisons. *Epidemiology.* 1990;1:43-46.

P Values

Sir.—In his article on *P* values[1] published in the April 1990 issue of *AJDC,* Brown has made some very helpful comments on the meaning of *P* values and has drawn attention to the difficulties associated with performing repeated statistical comparisons on the same set of subjects. However, twice in his article he does not pay sufficient heed to his own advice.

First, he correctly points out that when a *t* test is used to compare the birth weights of two groups of infants and the significant *P* value is set at .05, the random variation in birth weights among the infants would suggest, wrongly, in about one comparison of 20, that an important difference between the two groups in average weight was present. He goes on to consider what happens when a second test, eg, on head circumference, is performed on the same group, and says "The chance of 'significant' [it should read, "nonsignificant"] on the first test is .95. The chance on both the first and second is .95 × .95. The chance of 'significant' on either the first or second or both is $1 - .95^2 = .0975$."

However, the probability on both the first and second is .95 × .95 if the two tests are independent, which is most unlikely in the example given. Actually, the chance on both the first and second could have any value between .05 and .10 depending on the extent of dependence between the two events. Herein is a difficulty Brown has not mentioned: we do not know the effective change in *P* value when we perform a second test on the same group of individuals, because we do not know the extent of dependence between the two tests. It is because of this uncertainty that biostatisticians prefer a simultaneous evaluation that involves a *P* value that is known.

The purpose of these comments is not the trivial one of pointing out that there is a small statistical error in Brown's calculations, but the vital one of emphasizing his message even more strongly—that researchers must be wary of performing repeated tests on the same data. If they select a significance level of .05, the first test they perform *will* be at the .05 level, but subsequent tests *will not* be at that level, and decisions based on them are likely to be erroneous.

Second, Brown refers to a conundrum by O'Brien: "Suppose a clinical investigator at MegaClinic conducts a clinical trial on treatments A, B, and C in three groups of patients. At the conclusion of the trial, the data analyst might perform *three* comparisons: A vs B, A vs C, and B vs C. The well-trained analyst would see that the *P* value for each comparison should be adjusted downward from the overall $P \leq .05$. That is, he/she would penalize himself/herself for doing three statistical tests."

The point is that when the analyst, X, performs the first comparison (A vs B), there is no difficulty. When the second comparison, A vs C, is made, X is using the same group A as in the first comparison, and it is likely that the two comparisons are mutually dependent. The extent of dependence is unknown, and the *P* value effectively decreases by an unknown amount. When X performs the third comparison, B vs C, X is performing a test that is likely to have dependence with the first test, which used group B, and with the second test, which used group C. Hence, the *P* value should be adjusted, to an unknown extent, downward from the overall $P \leq .05$. The analyst *should* penalize himself/herself for doing three statistical tests.

On the other hand, "suppose that out in Podunk a study was conducted of just A vs B. Another investigator in Boondock studied A vs C. A third researcher in Foozball studied B vs C. They each used, quite appropriately, $P \leq .05$ for evaluating their two sample results. . . . Why should the investigator who has the most comprehensive overview of treatments A, B, and C be punished with an adjustment to the *P* value that is not imposed on the separate studies done in three less elaborate trials?" The answer is that, in the three separate studies, there is presumably no dependence between the tests performed and in the single study, there is likely to be unknown dependence.

If each group referred to in the "conundrum" consisted of 100 patients, altogether, 300 patients are in the first study. In the separate studies, each of the three comparisons involves 200 patients (ie, 600 patients altogether). As fewer patients are involved, we would expect the first investigation to be disadvantaged in some way compared with the second.

Analysts should heed Brown's warning that repeated statistical tests on the same elements or subjects introduce an increase in the risk of a type I error. In the same vein, Dr David Kleinbaum commented during a course on epidemiology held last year in Sydney, Australia, that "if you torture data sufficiently, they will eventually confess to something."

TED BYRT, MED
Clinical Epidemiology
and Biostatistics Unit
Royal Children's Hospital
Flemington Rd
Parkville, Victoria 3052,
Australia

1. Brown GW. *P* values. *AJDC.* 1990; 144:493-495.

Clavicular Fractures in Neonates: Frequency vs Significance

Sir.—I wish to thank Drs Joseph and Rosenfeld[1] for their evaluation of the frequency and presentation of clavicular fractures in newborns. This is useful information for "frontline" pediatricians like myself, but I would like to make the following comments.

The fact that the occurrence of newborn clavicular fractures has remained stable in the Western world during the past 85 years suggests to me that the New York State Health Department may be on the wrong track if it thinks that this is "an indicator of the quality of care."

Also, it seems that clavicular fractures are benign occurrences that virtually always heal well without intervention. The only reason then to diagnose clavicular fracture would be to explain irritability with motion or asymmetric Moro's reflexes. That suggests to me that, in children without these symptoms, there may be no reason to make a significant effort to make this diagnosis.

MICHAEL J. O'HALLORAN, MD
MIDELFORT CLINIC LTD
733 W Clairemont Ave
Eau Claire, WI 54702-1510

1. Joseph PR, Rosenfeld W. Clavicular fractures in neonates. *AJDC.* 1990; 144:165-167.

In Reply.—Dr O'Halloran points out that the New York State Health Department may be on the wrong track in using frequency of newborn clavicle fracture as a guideline for quality of care. By and large, we think he may be correct. In addition, the requirement for reporting newborn clavicle fractures in New York State may lead to unnecessary documentation and costs without any effect on the quality of care.

Dr O'Halloran also points out that the only reason to diagnose newborn clavicle fractures would be to explain symptoms, such as unexplained irritability. Another reason to diagnose newborn clavicle fractures is to prevent embarrassment at the first office visit when a large callus is felt covering the healthy broken clavicle. Additionally, we would prefer to make the diagnosis rather than to have the parent bring the callus to our attention on or before the first visit.

PAUL R. JOSEPH, MD
Warren Rosenfeld, MD
Department of Pediatrics
Winthrop-University Hospital
259 First St
Mineola, NY 11501

Clavicular Fractures in Neonates

Sir.—We read with interest the article by Joseph and Rosenfeld[1] in the February 1990 issue of *AJDC.* We have noticed an increased occurrence of clavicular fractures in our institution during the last 6 months (12 [1.48%] of 812 newborns). We looked at different variables, including maternal age, parity, infant's weight, maternal diabetes, length of labor, oxytocin (Pitocin) induction, delivery methods, local anesthesia, episiotomy, delivery time, and delivering physician (house staff or attending staff) to find the common factor(s) in these infants.

The only common factor for seven of the affected infants was a shorter second stage of labor (mean, 11.4 minutes). In contrast to the authors' observation that only one of the 18 infants showed "classic" physical findings, we diagnosed fractures in 11 of 12 infants by the palpation of instability or crepitation over the fracture site. Roentgenography was used to confirm our clinical diagnosis. In one case, two of us (G.C. and J.P.) and an orthopedist felt a subtle crepitation at the distal end of one clavicle; however, roentgenography failed to reveal a clear fracture.

We noticed that a small number of

our patients (3 of 12) required two examinations (the second examination on the second day of life) to make a diagnosis, whereas most of Joseph and Rosenfeld's patients were diagnosed on the second day. The exact frequency of clavicular fracture in the neonatal period is not known, but the rates reported by Farkas and Levine[2] (1.7%) and Enzler[3] (2.6%) seem to be reasonable estimations.

We would like to remind readers that clavicular fractures are not limited to large infants, who may require a prolonged second stage of labor. On the contrary, more than half of the affected infants in our institution were born after a rather precipitous labor. We believe a daily, thorough physical examination in the nursery, instead of a superficial examination in a hasty fashion, would enable us to detect almost all of the clavicular fractures while the infant is still in the nursery.

GLORIA CARTER, RN, PNP
JAY W. PARK, MD
Department of Pediatrics
CHARLES TARVIN, MD
Department of
Obstetrics/Gynecology
Texas Tech University
Health Sciences Center
Regional Academic
Health Center at Odessa
Odessa, TX 79763

1. Joseph PR, Rosenfeld W. Clavicular fractures in neonates. *AJDC.* 1990;144:165-167.

2. Farkas R, Levine S. X-ray incidence of fractured clavicle in vertex presentation. *Am J Obstet Gynecol.* 1950;59:204-206.

3. Enzler A. Die Claviculafraktur als Geburtsverletzung des Neugeborenen. *Schweiz Med Worchenschr.* 1950;80:1280-1283.

In Reply.—Carter et al make several excellent points. The most interesting is the observation that the second stage of labor was short for seven of the 12 newborns with clavicle fractures. It would be interesting to know the length of the second stage of labor for the other 800 infants without clavicle fractures. Unfortunately, we did not analyze our data with regard to the length of second stage of labor.

We also found it interesting that at one institution, Carter et al clinically found a high incidence (12 [1.5%] of 812 newborns) of newborn clavicle fractures. It would be interesting to know whether the 800 infants without clavicle fractures had been examined for evidence of clavicle callus at approximately 2 to 4 weeks of age.

PAUL R. JOSEPH, MD
WARREN ROSENFELD, MD
Department of Pediatrics
Winthrop-University Hospital
259 First St
Mineola, NY 11501

What About Gay Teenagers?

Sir.—We read with great interest and careful attention the two articles[1,2] that appeared in the June issue of *AJDC* highlighting preventive aspects of pediatric injury, including suicide. Both of these well-written and researched reports placed great emphasis on the preventability of injury, as well as intervention strategies and suggestions for further research. Indeed, such emphasis is a most significant aspect of pediatric and adolescent medical practice, and much of our office time is devoted to the education of children, teenagers, and their parents.

During our study of these articles, we found the omission of a most important topic, one that brings into focus the existence of the gay (homosexual) teenager. Although adolescent suicide, including the causes and suggestions for prevention, is discussed, the gay adolescent was not mentioned.

Gay teenagers most certainly exist. At least 10% of our country's population is gay, and there are approximately 2.9 million gay adolescents in the United States.[3] Not only do gay youth exist, but they are made quite vulnerable by prevailing societal attitudes toward gays. Some feel so badly about their sexuality and about themselves that suicide can become a possible solution to perceived problems.[4,5] According to the US Public Health Service,[6] gay youths are estimated to be two to three times more likely to attempt suicide as their heterosexual peers, and it is believed that as many as 30% of suicides annually are those of gay teenagers. This is obviously a most significant problem.

As health care providers, we need to be concerned about these teenagers. If health professionals can prevent just one adolescent suicide or help just one gay teenager feel good about himself or herself, then they will be doing well. Therefore, we wish to include the topic of the gay adolescent for serious consideration in intervention and research on the problem of adolescent suicide. This should include methods of helping health professionals recognize the existence and legitimacy of gay youth and to behave in ways that demonstrate to gay teenagers that they are valid and wholesome human beings.

We strongly believe that professionals in the field of pediatric and adolescent medicine should attempt to communicate to all their patients a humanistic acceptance of and respect for alternate life-styles and to treat gay teenagers with the dignity and respect they so justly deserve. We all need to convey the message that it is perfectly acceptable to be gay.

A network of community resources needs to be identified, including organizations and educational materials whose aim is to communicate to our youth that they are not alone, and that the very special feelings that our gay youth need to confront are valid and quite wholesome and good.

We hope that more research will be done and more articles written about ways to decrease pediatric and adolescent morbidity and mortality. We also hope that these reports will discuss and describe ways for health professionals to reduce the grave injury being done to 10% of our youth, much of which is fostered by societal silence and neglect.

CHARLES R. FIKAR, MD
MARY KOSLAP-PETRACO, BSN, RN
PO Box 306
Deer Park, NY 11729

1. Division of Injury Control, Center for Environmental Health and Injury Control, Centers for Disease Control. Childhood injuries in the United States. *AJDC.* 1990;144:627-646.

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6. Gibson P. Gay male and lesbian youth suicide. In: *Report of the Secretary's Task Force on Youth Suicide.* Washington, DC: US Public Health Service; 1989:3-110–3-142.

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References: 1. Data on file, Lederle Laboratories, Pearl River, NY. **2.** Neu HC: Beta-lactamase stability of cefixime. *Internal Medicine* 1990;11:57-71. **3.** A national study of consumer experience with antibiotic therapy. Princeton, NJ, The Gallup Organization, Inc., July 1989. Data on file, Lederle Laboratories, Pearl River, NY. **4.** Cockburn J, Gibberd RW, Reid AL, et al: Determinants of non-compliance with short term antibiotic regimens. *Br Med J* 1987;295:814-818. **5.** Hussar DA: Importance of patient compliance in effective antimicrobial therapy. *Pediatr Infect Dis J* 1987;6:971-975. **6.** Greenberg RN: Overview of patient compliance with medication dosing: A literature review. *Clin Ther* 1984;6:592-599. **7.** Neu HC, Chin N-X, Labthavikul P: Comparative *in vitro* activity and ß-lactamase stability of FR 17027, a new orally active cephalosporin. *Antimicrob Agents Chemother* 1984;26:174-180. **8.** Neu HC: *In vitro* activity of a new broad spectrum, beta-lactamase-stable oral cephalosporin, cefixime. *Pediatr Infect Dis J* 1987;6:958-962. **9.** Sanders CC: ß-lactamase stability and in vitro activity of oral cephalosporins against strains possessing well-characterized mechanisms of resistance. *Antimicrob Agents Chemother* 1989;33:1313-1317. **10.** Pichichero ME: Cefixime multicenter national otitis media study, in *The Contemporary Treatment of Otitis Media* 1990. Lederle Laboratories. Data on file, Lederle Laboratories, Pearl River, NY. **11.** Howie VM, Owen MJ: Bacteriologic and clinical efficacy of cefixime compared with amoxicillin in acute otitis media. *Pediatr Infect Dis J* 1987;6:989-991. **12.** Verghese A, Roberson D, Kalbfleisch JH, et al: Randomized comparative study of cefixime versus cephalexin in acute bacterial exacerbations of chronic bronchitis. *Antimicrob Agents Chemother* 1990;34:1041-1044. **13.** Kiani R, Johnson D, Nelson B: Comparative, multicenter studies of cefixime and amoxicillin in the treatment of respiratory tract infections. *Am J Med* 1988;85:6-13.

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In clinical trials of otitis media in nearly 400 children between the ages of 6 months and 10 years, *S pneumoniae* was isolated from 47% of the patients, *H influenzae* from 34%, *B catarrhalis* from 15%, and *S pyogenes* from 4%.

The overall response rate of *S pneumoniae* to cefixime was approximately 10% lower and that of *H influenzae* or *B catarrhalis* approximately 7% higher (12% when beta-lactamase positive strains of *H influenzae* are included) than the response rates of these organisms to the active control drugs.

In these studies, patients were randomized and treated with either cefixime at dose regimens of 4 mg/kg bid or 8 mg/kg qd, or with a standard antibiotic regimen. Sixty-nine to 70% of the patients in each group had resolution of signs and symptoms of otitis media when evaluated two to four weeks posttreatment, but persistent effusion was found in 15% of the patients. When evaluated at the completion of therapy, 17% of patients receiving cefixime and 14% of patients receiving effective comparative drugs (18% including those patients who had *H influenzae* resistant to the control drug and who received the control antibiotic) were considered to be treatment failures. By the two- to four-week follow-up, a total of 30% to 31% of patients had evidence of either treatment failure or recurrent disease.

Bacteriological Outcome of Otitis Media at Two- to Four-Weeks Posttherapy Based on Repeat Middle Ear Fluid Culture or Extrapolation from Clinical Outcome

Organism	Cefixime[a] 4 mg/kg bid	Cefixime[a] 8 mg/kg qd	Control[a] drugs
Streptococcus pneumoniae	48/70 (69%)	18/22 (82%)	82/100 (82%)
Haemophilus influenzae beta-lactamase negative	24/34 (71%)	13/17 (76%)	23/34 (68%)
Haemophilus influenzae beta-lactamase positive	17/22 (77%)	9/12 (75%)	1/1[b]
Moraxella (Branhamella) catarrhalis	26/31 (84%)	5/5	18/24 (75%)
Streptococcus pyogenes	5/5	3/3	6/7
All Isolates	120/162 (74%)	48/59 (81%)	130/166 (78%)

[a] Number eradicated/number isolated.

[b] An additional 20 beta-lactamase positive strains of *H influenzae* were isolated, but were excluded from this analysis because they were resistant to the control antibiotic. In 19 of these the clinical course could be assessed, and a favorable outcome occurred in 10. When these cases are included in the overall bacteriological evaluation of therapy with the control drugs, 140/185 (76%) of pathogens were considered to be eradicated.

Tablets should not be substituted for suspension when treating otitis media.

CONTRAINDICATIONS

Known allergy to cephalosporins.

WARNINGS

BEFORE THERAPY WITH SUPRAX IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEPHALOSPORINS, PENICILLINS, OR OTHER DRUGS. IF THIS PRODUCT IS TO BE GIVEN TO PENICILLIN-SENSITIVE PATIENTS, CAUTION SHOULD BE EXERCISED BECAUSE CROSS-HYPERSENSITIVITY AMONG BETA-LACTAM ANTIBIOTICS HAS BEEN CLEARLY DOCUMENTED AND MAY OCCUR IN UP TO 10% OF PATIENTS WITH A HISTORY OF PENICILLIN ALLERGY. IF AN ALLERGIC REACTION TO SUPRAX OCCURS, DISCONTINUE THE DRUG. SERIOUS, ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE TREATMENT WITH EPINEPHRINE AND OTHER EMERGENCY MEASURES, INCLUDING OXYGEN, INTRAVENOUS FLUIDS, INTRAVENOUS ANTIHISTAMINES, CORTICOSTEROIDS, PRESSOR AMINES, AND AIRWAY MANAGEMENT, AS CLINICALLY INDICATED.

Administer cautiously to allergic patients.

Treatment with broad-spectrum antibiotics alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of severe antibiotic-associated diarrhea including pseudomembranous colitis. Pseudomembranous colitis has been reported with the use of SUPRAX and other broad-spectrum antibiotics (including macrolides, semisynthetic penicillins, and cephalosporins). It is important to consider this diagnosis in patients who develop diarrhea in association with antibiotic use. Symptoms of pseudomembranous colitis may occur during or after antibiotic treatment and may range in severity from mild to life threatening. Mild cases usually respond to drug discontinuation alone. Moderate-to-severe cases should be managed with fluid, electrolyte, and protein supplementation. When the colitis is not relieved by drug discontinuance, or when it is severe, oral vancomycin is the drug of choice for antibiotic-associated pseudomembranous colitis produced by *C difficile*. Other causes of colitis should be excluded.

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ROSS Division of Abbott Laboratories, USA

PRECAUTIONS

General: Prolonged use may result in overgrowth of nonsusceptible organisms. If superinfection occurs, take appropriate measures.

Carefully monitor patients on dialysis. Adjust dosage of SUPRAX (cefixime) in patients with renal impairment and those undergoing continuous ambulatory peritoneal dialysis and hemodialysis. (See **DOSAGE AND ADMINISTRATION**.)

Prescribe cautiously in patients with a history of gastrointestinal disease, particularly colitis.

Drug Interactions: No significant drug interactions have been reported to date.

Drug/Laboratory Test Interactions: A false-positive reaction for ketones in the urine may occur with tests using nitroprusside but not with those using nitroferricyanide.

SUPRAX administration may result in a false-positive reaction for glucose in the urine using Clinitest®,** Benedict's solution, or Fehling's solution. Use glucose tests based on enzymatic glucose oxidase reactions (such as Clinistix®** or Tes-Tape®**).

A false-positive direct Coombs test has been reported during treatment with other cephalosporin antibiotics; therefore, it should be recognized that a positive Coombs test may be due to the drug.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Although no lifetime animal studies have been conducted to evaluate carcinogenic potential, no mutagenic potential of SUPRAX was found in standard laboratory tests. Reproductive studies revealed no fertility impairment in rats at doses up to 125 times the adult therapeutic dose.

Usage in Pregnancy: *Pregnancy Category B:* Reproduction studies have been performed in mice and rats at doses up to 400 times the human dose and have revealed no evidence of harm to the fetus due to SUPRAX.

There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery: SUPRAX has not been studied for use during labor and delivery. Treatment should only be given if clearly needed.

Nursing Mothers: It is not known whether SUPRAX is excreted in human milk. Consider discontinuing nursing temporarily during treatment with this drug.

Pediatric Use: Safety and effectiveness of SUPRAX in children aged less than 6 months have not been established.

The incidence of gastrointestinal adverse reactions, including diarrhea and loose stools, in pediatric patients receiving the suspension, was comparable to adult patients receiving tablets.

ADVERSE REACTIONS

Most adverse reactions observed in clinical trials were of a mild and transient nature. Less than four percent (3.8%) of patients in the US trials discontinued therapy because of drug-related adverse reactions. Commonly seen adverse reactions in US trials of the tablet formulation were gastrointestinal events, which were reported in 30% of adult patients on either the bid or the qd regimen. Clinically mild gastrointestinal side effects occurred in 20% of all patients, moderate events occurred in 9% of all patients, and severe adverse reactions occurred in 2% of all patients. Individual event rates included diarrhea 16%, loose or frequent stools 6%, abdominal pain 3%, nausea 7%, dyspepsia 3%, and flatulence 3%. The incidence of gastrointestinal adverse reactions, including diarrhea and loose stools, in pediatric patients receiving the suspension was comparable to adult patients receiving tablets.

Symptoms usually responded to symptomatic therapy or ceased when SUPRAX was discontinued.

Several patients developed severe diarrhea and/or documented pseudomembranous colitis, and a few required hospitalization.

The following adverse reactions have been reported following the use of SUPRAX. Incidence rates were less than 1 in 50 (less than 2%), except as noted above for gastrointestinal events.

Gastrointestinal: Diarrhea, loose stools, abdominal pain, dyspepsia, nausea, and vomiting. Several cases of documented pseudomembranous colitis were identified during the studies. The onset of pseudomembranous colitis symptoms may occur during or after therapy.

Hypersensitivity Reactions: Skin rashes, urticaria, drug fever, and pruritus. Erythema multiforme, Stevens-Johnson syndrome, and serum sickness have been reported rarely.

Hepatic: Transient elevations in SGPT, SGOT, and alkaline phosphatase.

Renal: Transient elevations in BUN or creatinine.

Central Nervous System: Headaches 3%; dizziness.

Hemic and Lymphatic Systems: Transient thrombocytopenia, leukopenia, and eosinophilia. Prolongation in prothrombin time was seen rarely.

Other: Genital pruritus, vaginitis, candidiasis.

The following adverse reactions and altered laboratory tests have been reported for cephalosporin-class antibiotics:

Adverse Reactions: Allergic reactions including anaphylaxis, toxic epidermal necrolysis, superinfection, renal dysfunction, toxic nephropathy, hepatic dysfunction, including cholestasis, aplastic anemia, hemolytic anemia, hemorrhage.

Several cephalosporins have been implicated in triggering seizures, particularly in patients with renal impairment when the dosage was not reduced (see **DOSAGE AND ADMINISTRATION** and **OVERDOSAGE**). If seizures associated with drug therapy occur, discontinue drug. Administer anticonvulsant therapy if clinically indicated.

Abnormal Laboratory Tests: Positive direct Coombs test, elevated bilirubin, elevated LDH, pancytopenia, neutropenia, agranulocytosis.

OVERDOSAGE

Gastric lavage may be indicated; otherwise, no specific antidote exists. Cefixime is not removed in significant quantities from the circulation by hemodialysis or peritoneal dialysis. Adverse reactions in small numbers of healthy adult volunteers receiving single doses up to 2 g of SUPRAX did not differ from the profile seen in patients treated at the recommended doses.

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Pediatric Legal Medicine

A New Venture

Medicine can no longer insist on dealing only with issues that relate to health and disease. Our educational, practice, and research efforts take place in a societal milieu that both reflects what we do and comments on it. Ethical, economic, social, and legal issues abound in society and affect us directly or indirectly. AJDC *has attempted to reflect these societal trends and influences by accepting or soliciting articles, editorials, letters, and commentaries on such topics. As Dr Ferry indicates in the following editorial,* AJDC *now is prepared to formalize one of these sets of issues, the legal environment in which we exist. As she states, this new department will be broad-based, not narrowly focused on any single issue. Articles will highlight some of the major legal issues in our communities. We look forward both to the inclusion of such information in the pages of our journal and to your responses as involved readers.*—V.A.F.

With this issue, *AJDC* inaugurates a new column, "Pediatric Legal Medicine." The stimulus for this column was a lunch in Bethesda, Md, in the fall of 1989, when my respected colleague Karin Nelson, MD, suggested, "Isn't it time a leading pediatric journal had a specific column on legal issues affecting children and pediatricians?" Both of us agreed that, over the years, legal considerations have had a serious impact on the practice of pediatrics.

As noted in a recent textbook, *Legal Aspects of Medicine*, "There is hardly a physician who has not been deeply troubled by legal problems professionally, economically, and, most important of all, psychologically."[1]

The concept was presented to the *AJDC* Editorial Board at its Spring 1989 meeting in Chicago, Ill, and enthusiastically endorsed. Strong caveats were issued, however, that the new forum should not just be a "malpractice column" but should reflect broader issues relating to children and the law in today's society.

See also p 275.

To assist in the development of this new enterprise, I have asked a small sub-board of knowledgeable individuals to assist me. These include Eileen Ouellette, MD, a pediatric neurologist at Massachusetts General Hospital, Boston, who recently completed her law degree and will specialize in medicolegal issues affecting children; Lynn D. Fleisher, PhD, JD, a Chicago attorney/geneticist who has written previously in *AJDC* on wrongful births and liability for prenatal injury[2]; and Robert L. Brent, MD, from the Department of Pediatrics, Jefferson Medical College, Philadelphia, Pa, who has written and spoken out forcefully on a number of medicolegal issues, particularly the inappropriate expert witness.[3] In addition, I have asked William O. Robertson, MD, from the Department of Pediatrics, University of Washington Medical School, Seattle, to serve as liaison between the new column and the Medical-Legal Section of the American Academy of Pediatrics, Elk Grove Village, Ill.

Topics for further discussion in the new forum include the rights of children and whether they are being met, emerging trends in the legal aspects of child abuse, management of children in persistent vegetative states, current aspects of "baby Doe" legislation, handgun legislation, child care legislation, problems of drug abuse (rights of children vs mothers), and discussion of pediatric malpractice cases (review of expert witness testimony, psychological aspects of the pediatrician being sued, etc).

In addition, we will offer periodic book reviews, editorial commentaries, and other relevant material as deemed appropriate. We welcome readers' suggestions, comments, and ideas. The main purpose of the new forum is to provide education and improve knowledge and communication about this important area of the practice of pediatrics and the care of children and families.

Peggy C. Ferry, MD
Department of Pediatrics
University of Arizona
Health Science Center
1501 N Campbell
Tucson, AZ 85724

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Pediatric Perspectives

Vistas and Vantage Points

According to *Webster's*, a perspective affords one the opportunity to make an accurate evaluation by observing things in their true relationships. Perhaps this includes a new view, a vista, from which the observer can stand back, observe, and get unique, refreshing new insights into common (and not so common) occurrences.

Pediatric Perspectives is a relatively new addition to *AJDC*'s special departments, which include Research to Relevance, Educational Interventions, Sports Medicine, and others. In this department, we hope to provide our readers with new insights into, and innovative ways of viewing, pediatric medical topics while providing learned treatises on current forces and issues that affect the everyday practice of pediatrics by all physicians, from the general practitioner to the teacher/clinician to the research scientist. For example, in this issue of *AJDC*, Elaine Wyllie, MD, discusses advances in diagnosis of and therapies for seizure disorders as they relate to central nervous system surgery.

per·spec·tive (per-spek´ tiv), adj. [ME. <LL. *perspectivus* <L. *perspicere*, to look through <*per*, through + *specere*, to look.] **1.** the art of picturing objects or a scene in such a way, eg, by converging lines as to show them as they appear to relative distance or depth **2.** the appearance of objects or scenes as determined by their relative distance and positions **3.** the relationship or proportion of the parts of a whole, regarded from a particular standpoint or point in time **4.** a specific point of view in understanding or judging things or events, esp. one that shows them in their true relation to one another b) the ability to see things in a true relationship[1]

See also p 314.

Pediatrics in the 1990s faces many issues that require immediate attention. For example, the exponential increase in knowledge of biochemical genetics has allowed prenatal detection of a number of inherited metabolic diseases, such as Tay-Sachs disease. Perhaps soon, medical practices will incorporate new therapies, such as genetically engineered prenatal treatment (eg, insertion of particular genes into a developing embryo's existing genetic material).

As neonatal intensive care becomes increasingly refined and complex, we may see the end of classic respiratory distress syndrome as a pathophysiologic entity because of the use of exogenous surfactant, but has this medical advance allowed the smallest, most fragile infants to survive who otherwise might have died? Are increasing numbers of infants living, but with long-term, chronic disabilities, such as retinopathy of prematurity or neurologic impairment?

Issues such as these are representative topics that can be addressed in Pediatric Perspectives. We invite pertinent "state-of-the-art" reviews. We also invite scholarly opinion pieces—those that provide unique approaches to difficult or common issues. Pediatric Perspectives is a medium for bringing readers up to date on new advances and for providing refreshing observations from new vantage points.

Alan D. Bedrick, MD
Department Editor,
Pediatric Perspectives *AJDC*

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Your Child's Best Friend: TV or Not TV

E. Richard Stiehm, MD

"Dick" Stiehm and I have been colleagues and friends for a long time, dating back to the golden days at Philadelphia (Pa) General Hospital, when we were both interns. We have authored a text together and dealt with similar issues in our research careers. Dick has been a valuable contributor to AJDC, *offering his insightful critiques on articles, suggesting ways that the journal could be improved, soliciting state-of-the-art articles for us, and offering nonmedical observations that stimulate our readers to respond. His contribution at right continues this last-named tradition.*

Dick is one of the most respected pediatric immunologists in the world. He is regarded as an expert in many areas, and his work has influenced the use of immunoglobulin therapy, particularly the newer intravenous preparations. He has contributed to our understanding of congenital and acquired immunodeficiencies, to our knowledge and use of vaccines, and to the unraveling of basic immunologic mechanisms. He is a prolific contributor to medical literature, both in scientific publications and in educational materials, such as the third edition of the textbook **Immunologic Disorders in Infants and Children** *(Philadelphia, Pa: WB Saunders Co; 1989). This is the definitive text in this area and Dick's skillful editing and writing have made it the most up-to-date, authoritative source for basic immunologic understanding and clinical applications.*

Would you like your children's best friend to monopolize 3 to 4 hours of their time every single day, discourage their participation in sports, prevent them from playing the piano or learning anything about classical music, interfere with their homework, and steal every book that they might want to read?

Well, I did not like my three daughters' best friend at all. Moreover, I had grave doubts about their friend's attitudes on sex, drugs, violence, and materialism. So I got rid of it. I banished TV!

All surviving parents have a list of things they believe they did right with their children, and a larger list, often repressed, of minor "boo-boos" and major catastrophes. The latter are too painful for me to resurrect. But three things I (we) did right were (1) to insist on music lessons; (2) to use a "magic apple" to cure all nightmares and bedtime insomnia (an apple slice anointed with the magic properties of "putting you to sleep within 10 minutes"); and (3) to abolish all TV privileges. My only concession was 1 hour on Friday and Saturday nights, and the nightly network news (which they did not watch).

I did it, in part, for selfish reasons. I wanted to listen to my music at night. But more importantly, I had the feeling that my first two daughters were shortchanging their schoolwork, their reading, and their music for their allotted nightly half-hour, "PTA-approved" TV program. And I was endlessly monitoring their viewing: "No, it's not my half hour, it's Carrie's!" "Why are these people killing each other?" "Jamie won't let me watch my program." "Why can't we have a Mercedes and a swimming pool?" About the time my two oldest girls were 12 and 10 years of age, I said, "Enough! No more TV!"

I was immediately branded the "meanest and strictest father in Santa Monica." Some wise pediatrician once told me that if your children do not think you are the strictest parent in the neighborhood, you are not strict enough. I reminded my girls that their piano teacher and her husband, who had three children too, did not even *have* a TV.

After a month or so, my girls realized I was not giving in, so they stopped sulking and started to do other things, like their schoolwork, playing the piano, reading, banging tennis balls against the garage door, and—would you believe it—listening to Brahms and liking it!

Our Saturdays did not start with 2 hours of cartoons. After their assigned chores, they were out all day playing tennis or soccer or spending time with real live friends (possibly at their house watching TV!). At any rate I did not have to put up with the banality of those awful, often violent, cartoons.

Our third and youngest daughter, who grew up with a "no TV" policy, never had TV withdrawal. She thought TV broadcasting stopped at 7:30 PM after the Evening News With Dan Rather and did not resume until Friday night.

There are a few disadvantages to a "no TV" policy. For one thing, you (the parents) cannot watch; for another, your children will be unable to answer the questions in the entertainment category of Trivial Pursuit (but they will be better at every other category); third, you will have to endure their stories about how excluded they felt from their friends' conversation at school about the previous night's programs; finally, *you* will have to pay more attention to your children because their best friend is not monopolizing all their time. But these are minor disadvantages compared with the multiple advantages.

My grown daughters, now in their 20s, today acknowledge that they got along "OK" without their best friend and do not want that friend for their own children.

The Pediatric Branch, National Cancer Institute in Bethesda, Maryland, has over two dozen active treatment protocols for a wide variety of pediatric malignancies including diseases such as acute leukemia, non-Hodgkin's lymphoma, Ewing's sarcoma, osteogenic sarcoma, rhabdomyosarcoma, neuroblastoma and brain tumors. There is also an active treatment program for children with HIV disease. The Pediatric Branch has a 26-bed inpatient unit and extensive outpatient services including "day hospital" facilities. Children with newly diagnosed or recurrent malignancies, may be eligible for treatments.

Emphasis is placed on maintaining close communication and cooperation with referring physicians. **For more information on patient oncology or HIV referrals, please call collect (301) 402-0696.**

NATIONAL CANCER INSTITUTE
PEDIATRIC BRANCH

A Public Service Announcement Courtesy of this Publication

Standardized Percentile Curves of Body-Mass Index for Children and Adolescents

Lawrence D. Hammer, MD; Helena C. Kraemer, PhD; Darrell M. Wilson, MD;
Philip L. Ritter, PhD; Sanford M. Dornbusch, PhD

• Weight-for-height indexes are often used in the clinical assessment of obesity in children and adolescents. The direct measurement of adiposity, using hydrostatic weighing and other techniques, is not feasible in studies involving young children or with large numbers of older subjects. Ratios of weight relative to height, such as the body-mass index (weight/height²), may be used as indirect measures of obesity and correlate with more direct measures of adiposity. Using data from the First National Health and Nutrition Examination Study, 1971 to 1974, standardized percentile curves of body-mass index for white children and adolescents were developed. These curves may be used to monitor the body-mass index of white children and adolescents longitudinally and for comparing an individual with others of the same sex and age.

(*AJDC.* 1991;145:259-263)

Obesity is a significant health problem, with medical and psychological consequences for children and adolescents.[1-3] Obesity is best defined as a condition of excessive adiposity. Several methods are available for estimating adiposity, including measurement of body density using underwater weighing, estimation of lean body mass using deuterium distribution, and estimation of lean body mass by measurement of potassium 40 levels. Although these methods are considered to be "gold standards," they are based on assumptions regarding body density and lean body mass inferred from studies largely involving adults. Limitations in the validity of these methods are reviewed by Lohman.[4] Furthermore, these techniques are technically difficult to apply to children and are impractical in most clinical settings. Therefore, "indirect" measures of adiposity, such as skinfold thickness and weight-for-height indexes, are often used as proxy measures of adiposity or as criteria for defining obesity.[5]

Inconvenience and inaccuracy in the measurement of skinfold thickness and variability in the distribution of subcutaneous fat limit the use of this measure in many clinical settings.[6,7] The body-mass index (BMI), known also as the Quetelet Index,[8] is often used as an index of overweight in children[9,10] and is more easily obtained than measurement of skinfold thickness. For any index of overweight to be meaningful in the pediatric age group, there must be standards defined by age, sex, and race, since adiposity is known to vary with these factors.[11] We therefore developed percentile curves of BMI for white males and females, aged 1 to 19 years, using data from a national sample, representative of the noninstitutionalized population of the continental United States.

SUBJECTS AND METHODS

The First National Health and Nutrition Examination Survey, 1971 to 1974 (NHANES I), was conducted for the purpose of gathering data regarding the nutritional and health status of the American population.[12] NHANES I includes data from a stratified probability sample, representative of the noninstitutionalized civilian population of the continental United States. These data were made available on computer tape from the National Center for Health Statistics, through the Interuniversity Consortium for Political and Social Research. Included in NHANES I are data from 5679 white individuals, aged 1 to 19 years. Only whites were included in the following analyses, since the distribution of BMI varies by race,[13] and the data set does not include a sufficient number of nonwhite children aged 1 through 19 years to allow development of age- and gender-specific standardized percentile curves.

Each subject in NHANES I underwent a complete physical examination, a detailed medical and nutritional history, and a variety of laboratory tests. Included in the physical examination were measurements of height and weight. The methods for obtaining these measurements are described in detail elsewhere.[12,13]

Each subject was assigned a Poverty Index score, based on the family's income and size[12]; we used this score as an index of social class. The effect of social class on BMI was examined and the correlation between social class and BMI was found to be nonsignificant in each age group and for the overall sample. For this reason, the group percentiles within each social class were not calculated and BMI distributions were not adjusted for social class.

Smoothed percentile curves of BMI by age were developed using raw data from the NHANES I (Figs 1 and 2). These curves were drawn by fitting unique quadratic models for the lower (males aged 1 to 11 years, females aged 1 to 13 years) and upper (males aged 8 to 19 years, females aged 6 to 19 years) portions of each curve. These quadratic models were then spliced and smoothed separately for males and females (males spliced at age 10 years, females at age 7 years). All procedures were done using the SAS.[14]

RESULTS

The Table contains the smoothed percentile values of BMI for white males and females, for ages 1 to 19 years, based on data from the NHANES I survey. Smoothed percentile curves of these data are presented in Figs 1 and 2.

Accepted for publication October 29, 1990.

From Stanford University School of Medicine, Palo Alto, Calif.
Reprint requests to Children's Hospital at Stanford, 520 Sand Hill Rd, Palo Alto, CA 94304 (Dr Hammer).

Percentile Values of Body-Mass Index, NHANES I*

	Percentile						
Age, y	5	10	25	50	75	90	95
			Males				
1	14.6	15.4	16.1	17.2	18.5	19.4	19.9
2	14.4	15.0	15.7	16.5	17.6	18.4	19.0
3	14.0	14.6	15.3	16.0	17.0	17.8	18.4
4	13.8	14.4	15.0	15.8	16.6	17.5	18.1
5	13.7	14.2	14.9	15.5	16.3	17.3	18.0
6	13.6	14.0	14.7	15.4	16.3	17.4	18.1
7	13.6	14.0	14.7	15.5	16.5	17.7	18.9
8	13.7	14.1	14.9	15.7	17.0	18.4	19.7
9	14.0	14.3	15.1	16.0	17.6	19.3	20.9
10	14.2	14.6	15.5	16.6	18.4	20.3	22.2
11	14.6	15.0	16.0	17.2	19.2	21.3	23.5
12	15.1	15.5	16.5	17.8	20.0	22.3	24.8
13	15.6	16.0	17.1	18.4	20.8	23.3	25.8
14	16.1	16.6	17.7	19.1	21.5	24.4	26.8
15	16.6	17.1	18.4	19.7	22.2	25.4	27.7
16	17.2	17.8	19.1	20.5	22.9	26.1	28.4
17	17.7	18.4	19.7	21.2	23.4	27.0	29.0
18	18.3	19.1	20.3	21.9	24.0	27.7	29.7
19	19.0	19.7	21.1	22.5	24.4	28.3	30.1
			Females				
1	14.7	15.0	15.8	16.6	17.6	18.6	19.3
2	14.3	14.7	15.3	16.0	17.1	18.0	18.7
3	13.9	14.4	14.9	15.6	16.7	17.6	18.3
4	13.6	14.1	14.7	15.4	16.5	17.5	18.2
5	13.5	14.0	14.6	15.3	16.3	17.5	18.3
6	13.3	13.9	14.6	15.3	16.4	17.7	18.8
7	13.4	14.0	14.7	15.5	16.7	18.5	19.7
8	13.6	14.2	15.0	16.0	17.2	19.4	21.0
9	14.0	14.5	15.5	16.6	18.0	20.8	22.7
10	14.3	15.0	15.9	17.1	19.0	21.8	24.2
11	14.6	15.3	16.2	17.8	19.8	23.0	25.7
12	15.0	15.6	16.7	18.3	20.4	23.7	26.8
13	15.4	16.0	17.1	18.9	21.2	24.7	27.9
14	15.7	16.4	17.5	19.4	21.8	25.3	28.6
15	16.1	16.8	18.0	19.9	22.4	26.0	29.4
16	16.4	17.1	18.4	20.2	22.8	26.5	30.0
17	16.9	17.6	18.9	20.7	23.3	27.1	30.5
18	17.2	18.0	19.4	21.1	23.7	27.4	31.0
19	17.5	18.4	19.8	21.4	24.0	27.7	31.3

*NHANES I indicates National Health and Nutrition Examination Survey, 1971 to 1974.

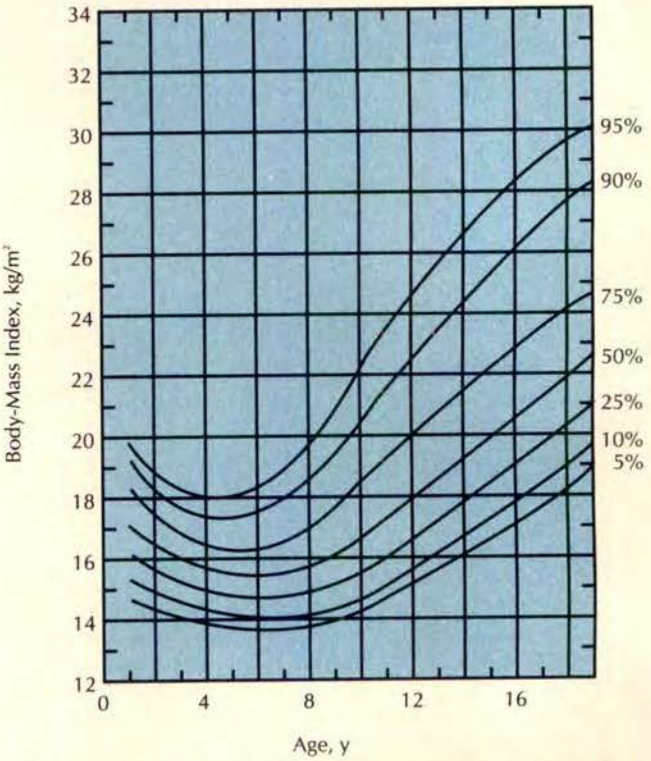
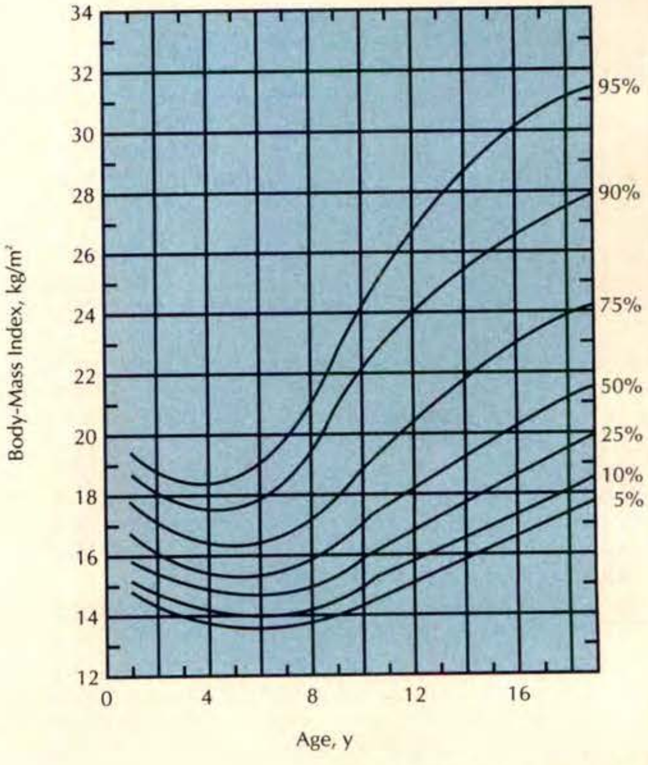


Fig 1.—*Body-mass index for white males aged 1 to 19 years. Percentiles were computed using data from the First National Health and Nutrition Examination Survey, 1971 to 1974.*

Fig 2.—*Body-mass index for white females aged 1 to 19 years. Percentiles were computed using data from the First National Health and Nutrition Examination Survey, 1971 to 1974.*



As previously reported, changes in BMI in early childhood are similar for males and females.[8,13] The BMI decreases from the age of 1 year until 4 to 6 years, when a trough occurs, after which BMI increases again.

Although the shapes of the curves for males and females are similar, the percentile values for BMI differ considerably in males and females at some ages. For the fifth to 75th percentiles, BMI values for males and females differ by less than 0.5 kg/m^2 between the ages of 1 and 14 years. After age 14 years, the fifth to 75th percentile values of BMI for males exceed those for females by as much as 1.5 kg/m^2.

The upper percentiles (90th to 95th) at the age of 1 year are higher for males than for females. From the age of 2 through 5 years, male-female differences in BMI are again less than 0.5 kg/m^2 at these upper percentiles. From age 6 years to 14 years, values of BMI for females exceed those for males, at these upper percentiles, by more than 0.5 kg/m^2. This trend continues in the 15- to 19-year age group, at the 95th percentile, with females having greater values of BMI than males.

COMMENT

Indicators of overweight are useful in the diagnosis and management of obesity in childhood and adolescence. An index of overweight that can be employed across all age groups would be ideal. Direct measures of adiposity, such as hydrostatic weighing, total body potassium determination, and deuterium distribution, are of only limited usefulness, owing to their cost, risk, inconvenience, and questionable validity, especially when applied to children and adolescents. On the other hand, BMI has been shown to have utility as an index of obesity during childhood[9] and adult life[13] and to be predictive, in childhood, of later obesity.[15] In a two-decade follow-up study, Rolland-Cachera et al[16] found that correlations between measures of BMI performed annually from 1 through 16 years of age and BMI at follow-up (18 to 25 years of age) exceeded the correlations between measures of skinfold thickness at four sites (individually or combined) taken annually during childhood and at follow-up, both for males and for females.

Skinfold thickness has often been used as a measure of adiposity in children and adolescents. Some investigators have used skinfold thickness as a gold standard against which other measures of obesity have been judged[17]; however, there are problems with skinfold thickness as a measure of either adiposity or obesity. Skinfold thickness is usually measured at only a limited number of sites and only reflects site-specific subcutaneous fat deposition[18]; moreover, the distribution of subcutaneous fat varies widely by age, sex, race, and body habitus.[19,20] Reference standards for skinfold thickness are available for only a limited number of sites. Furthermore, measurement of skinfold thickness in children, even when performed by trained personnel, may be unreliable, owing to interobserver error[21] and technical difficulty, especially in young children.[13] Measurements made using different types of calipers may also differ significantly.[22,23] The validity of skinfold measures as measures of adiposity or obesity may be even lower in obese subjects, in whom accuracy of measurement has not been adequately studied.[21] Finally, variation in subcutaneous fat distribution limits skinfold thickness as a predictor of risk secondary to obesity.[24]

Height and weight measurements are routinely performed in the clinical care of children and are monitored throughout childhood and adolescence as indicators of health and disease.[25] Accurate measurements of height and weight can be obtained using readily available instrumentation such as the stadiometer or, for children less than 3 years of age,[25] a supine measuring table for length and an appropriately calibrated scale for weight.[26] Furthermore, the impact of error in height measurement is minimized in the calculation by using height expressed in meters, since any error is placed in the second decimal column.

Although BMI ratios using various values of the exponent P in the ratio weight/height^P have been studied, where P may vary with gender, race, or other characteristics, noninteger values of P are clumsy to use in calculating weight/height^P in the clinical setting and offer little advantage over the ratio weight/height^2.[26] The BMI calculated as weight/height^2 is highly correlated with skinfold thickness in adult men and women[27] and in children and adolescents 4 through 17 years of age.[28] Despite the limitations of BMI as a measure of adiposity,[29] BMI remains a clinically useful index of weight relative to stature.[23] That BMI may reflect increased lean body mass as well as body fat[29] is appropriate, given that individuals who are fatter are likely to have more lean body mass and to be taller than individuals who are thinner, a pattern often observed during childhood and adolescence.[30]

The BMI is an easily calculated index. However, a nomogram for determining BMI has been previously published,[31] and tables for determining BMI (as kilograms per square meter) from measures of height and weight in inches and pounds are also available.[24]

The standardized curves of BMI offer an opportunity to monitor an individual's degree of obesity from childhood through adolescence. The Table contains the smoothed values of BMI used in plotting Figs 1 and 2. These values are similar to those published previously for males and females over the age of 6 years[13] and include newly smoothed values for children under 6 years of age. Although based on cross-sectional data, these curves follow the developmental pattern observed in longitudinal studies of BMI.[9,15] These curves may be used clinically as a means of monitoring relative change in BMI over time, as is routinely done in clinical practice for weight, height, and head circumference.[32] Use of a single computed measure simplifies the process of monitoring change in weight relative to change in height. Limitations in the use of cross-sectionally derived weight and height curves would also apply to these BMI curves.

The pattern of BMI over time has clinical significance. Longitudinal studies in childhood have demonstrated a developmental pattern of BMI. The age at which the trough in BMI occurs (4 to 8 years) is a potent predictor of later obesity, with children having an increased risk of later obesity if their BMI trough ends and the adiposity rebound begins before 5.5 years.[15] Though these BMI curves have been derived from cross-sectional data, the trough in the upper percentiles occurs earlier than the trough in the lower percentiles. This would suggest that children whose BMI falls in the upper percentiles may be more likely to have their adiposity rebound occur early. Furthermore, BMI has predictive value in adults with respect to morbidity and mortality.[24]

It is known that with the onset of adolescence and puberty, the adiposity of males and females increases, with females becoming increasingly fat compared with males. The use of skinfold thickness as a measure of body fatness may exaggerate the difference in adiposity between males and females,[33] since that difference can be partly explained by differences in fat distribution (including internal-external fat ratio) and gender-specific essential fat.[21]

The absence of large differences in BMI for males and females at each age may be due to the higher correlation of BMI with total body fat than with percentage of body fat[31]; total body fat is known to increase in both males and females through adolescence.[34,35] Higher values of BMI for males than females older than 14 years of age in the fifth through 75th percentiles may also be explained by the greater increase in lean body mass seen in males in this age group.

Percentile values for precisely defining obesity based on BMI or other measures remain to be determined. These cutoff points should be based on levels of BMI above which the morbidity related to obesity is known to occur. Though any degree of overweight may carry risk,[24] a definition of obesity based on BMI would be most useful if levels of BMI (by age and sex) that carry increased risk can be specified. For example, it has been suggested that adult men with BMI greater than 27.2 and adult women with BMI greater than 26.9 are at increased risk for morbidity and mortality.[24] These curves of BMI provide a clinical tool for monitoring BMI as children approach adult life. Further research is needed to provide a clearer picture of the relative risks associated with increased BMI at each age level for boys and girls. An additional use of the BMI as an index of obesity would arise from longitudinal research demonstrating the relative risk of long-term obesity associated with increased levels of BMI at particular ages in childhood.

The NIH Consensus Development Conference on Obesity has recommended use of the 85th percentile (weight for height) as a cutoff point for obesity in adults. For clinical purposes, we have found the 95th percentile BMI to be a conservative cutoff point for defining obesity in childhood. Following the BMI pattern provides more useful clinical information, however, than any single measurement of BMI. Further studies are needed to define useful criteria for defining obesity using BMI in childhood and adolescence. These studies should consider the morbidity associated with increasing percentile levels of BMI, including increased risk for long-term obesity.

A potential criticism of this study is that it relies on data from a national survey that oversampled from among lower socioeconomic groups in the United States. The effect of social class on BMI in this sample was examined and found to be nonsignificant within each age group and for the overall sample. For this reason, the group percentiles within each social class were not recalculated, nor were the distributions of BMI adjusted for social class.

CONCLUSION

Standardized curves of BMI were developed for white males and females by smoothing data from a large, stratified sample of 1- through 19-year-olds in the United States. These curves may be used to monitor the development of obesity as well as changes in BMI associated with treatment of obesity in childhood and adolescence. Since the pattern of BMI has been shown to be a predictor of long-term obesity in childhood, and to predict morbidity and mortality in adulthood, it is recommended that clinicians routinely measure height and weight and monitor BMI in caring for children and adolescents. Using appropriate data sets, such curves should also be developed for other racial groups. Further studies are needed to define appropriate cutoff points of BMI for more precisely defining obesity in childhood and adolescence.

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Improved Speed and Accuracy of Calculations With a Programmable Calculator in Pediatric Emergency Scenarios

Marlene Melzer-Lange, MD; David Wyatt, MD; Christine Walsh-Kelly, MD; Douglas Smith, MD; Mary A. Hegenbarth, MD; Carl S. L. Eisenberg, MD

• Both mathematical and selection errors may occur when ordering drug or fluid therapy in a busy emergency department. In an attempt to improve the speed and accuracy of such calculations, we programmed a hand-held calculator to assist in drug and intravenous fluid therapy dosages and rates for three emergency situations: diabetic ketoacidosis, asthma, and asystole. Performance by 58 subjects at various levels of training was compared when using either the programmable calculator or standard materials and methods. When standard methods were used, an average of 30.6 minutes was needed to complete the three scenarios, with an accuracy of 73%; by contrast, use of programmable calculator resulted in a significant decline in time needed to calculate doses (an average of only 8.5 minutes), with an improved accuracy of 98%. The use of a programmable calculator can result in a significant improvement in both speed and accuracy of drug and fluid selection and dosage and rate calculations, regardless of the level of the subject's medical training.

(*AJDC*. 1991;145:264-266)

Pediatric emergencies present special challenges to the physician. Children vary widely in weight, age, and biological maturity. These variables influence the selection of drug and fluid therapy. Initial selection and subsequent rate and dose calculations for therapy of the critically ill child can be especially difficult under the pressure of an emergent situation. Through experience, the pediatric emergency specialist may develop the facility to effectively handle the great majority of such emergencies; for other physicians or residents caring for children in a general emergency department, these calculations may be more difficult due to unfamiliarity.

Several authors have presented guidelines to simplify this situation. *The Harriet Lane Handbook*[1] is a traditional pediatric reference that has long given standards for fluid and drug therapies for children. Losek and Garland[2] published *The First Five Minutes,* which lists precalculated doses of drugs used to resuscitate critically ill children based on patients' body weights. Computerization of such guidelines has also been developed. Kelly et al[3] described the use of a programmable calculator for calculation of pediatric vasopressor drugs. Yamamoto and Wiebe[4] devised a computer program (for an IBM-PC compatible computer) that gives guidelines and calculates weight-appropriate doses for adult and pediatric patients.

We compared the use of a programmable calculator with more traditional methods for calculating weight and age doses of specific fluids and medications used in three common pediatric emergencies. The intention of this study is to examine whether a programmable calculator aids physicians in their capacity to rapidly and accurately calculate fluid and drug doses for common pediatric emergencies.

METHODS

Fifty-eight physicians and medical students took two sequential written tests. Each test consisted of a set of three common pediatric emergency scenarios: asystole, acute asthma, and diabetic ketoacidosis. Each scenario consisted of a brief case history and used a fill-in-the-blank or short answer format. The scenarios in each test set were of comparable difficulty, varying only in details such as patient's age and weight. The asystole scenario required calculation of resuscitation and maintenance fluids; endotracheal tube size; a single dose of epinephrine hydrochloride, atropine sulfate, and sodium bicarbonate; and instructions for preparation of a dopamine hydrochloride infusion. The asthma scenario required calculation of maintenance fluids, an intravenous aminophylline bolus based on the patient's weight and serum aminophylline level, a maintenance aminophylline infusion based on the patient's age, a methylprednisolone bolus infusion, and mixing instructions and flow rate for an isoproterenol hydrochloride infusion. The diabetic ketoacidosis scenario required calculation of the initial 2 hours of replacement fluid (amount and type), insulin infusion (amount and type), and serum osmolalities.

Each subject took one test set using the programmable calculator and one test set using a pocket calculator, a *Harriet Lane Handbook,*[1] and the Children's Hospital of Wisconsin guidelines routinely available to all physicians who have rotations in the emergency department. Ranges of correct answers to all questions were based on these standard therapeutic guidelines. To negate any potential bias due to learning effects, subjects were randomly assigned to first use either the programmable calculator or the standard materials. Randomization was performed by sequential assignment to a list of computer-generated random numbers. The tests were administered without interruption to single subjects under supervision either in a room with tape-recorded emergency department background noise or in the emergency department itself. Times required for each test set were recorded.

The programmable calculator (model 42S, Hewlett-Packard Company, Corvallis, Ore) (Figure) is a small 140-g hand-held, battery-operated model with 7 kilobytes of memory and more

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From the Medical College of Wisconsin, Children's Hospital of Wisconsin, Milwaukee.

Reprint requests to Department of Pediatrics, 9000 W Wisconsin Ave, MS 756, Milwaukee, WI 53226 (Dr Melzer-Lange).

Programmable calculator with menu display.

than 350 internal functions. It has an automatic four-level memory stack, can store both α-strings and numeric variables, is capable of program branching, and can accept and test user input from the keyboard. The two-line liquid crystal display is 22 characters wide, can display both uppercase and lowercase letters with punctuation, and can show a customized menu. This allows effective prompting of the user, and the calculator program can lead the subject through the questions in each of the scenarios. The subject chooses the scenario from a menu and provides input as requested in the display. The program pauses after each calculation is displayed and is restarted by the user after the answer has been noted. Subjects quickly learn to use the calculator after a standard 2-minute demonstration.

For statistical comparison, subjects were divided into seven groups based on the degree and type of training: private practice pediatricians, first-year (PL-1) and third-year (PL-3) pediatric residents completing their respective year of training, emergency medicine residents at all levels of training, second-year family practice residents, third-year medical students on their first pediatric rotations, and fourth-year medical students on elective pediatric rotations.

Numerical answers were considered correct if they were within 10% of the expected value. Failure to indicate a fluid or insulin type, incorrect fluid type, or no answer given were considered incorrect answers. There were 27 questions in each test set. Scores were calculated as the percentage of correct answers.

Analysis of variance techniques were used to evaluate differences in mean times between the seven subject groups for each method. Statistical analysis was also performed for the difference in total time required between the two methods for each individual physician. Two-sided paired *t* tests were used to test the significance of this difference within each physician group. Analysis of variance was performed to assess overall significant difference between physician groups with Tukey-Sidak's tests employed for pairwise comparisons between these groups. We used χ^2 tests to evaluate differences in accuracy between the methods.

RESULTS

The PL-3 group had the shortest time required to complete the test set using standard methods. One subject in the PL-1 group was excluded from the study; the prolonged time (103.9 minutes) required to complete the calculations using the standard method was 6 SDs beyond the mean. There was an overall significant difference for time among the subject groups using the standard method ($P = .0427$), with a significant difference between the PL-1 and PL-3 groups (Table 1). There were no significant differences for time among the subject groups using the programmable calculator. In addition, there was an overall significant difference between the time required to complete the scenarios with the programmable calculator vs the standard method ($P = .0067$), as well as a significant difference between the PL-3 group and both the PL-1 group and attending physicians. This means that the improved time in both the PL-1 and attending physician groups was significantly greater than in the PL-3 group. There was no significant difference in mean times based on method first employed. Failure to show significance could be due to small sample sizes. Each subject group showed significant speed improvements with the programmable calculator. Accuracy was also significantly improved using the calculator (Table 2). Ninety-eight percent of the answers were correct with the programmable calculator vs 73% of the responses using standard methods ($P < .0001$).

Table 1.—Time (Minutes) Needed to Complete Calculations*

Group†	No. of Subjects	Standard Method	Calculator	Difference
MS-3	10	35.1 ± 9.9	9.89 ± 2.6	25.3 ± 9.4
MS-4	10	31.9 ± 9.4	9.0 ± 4.1	22.9 ± 9.4
FP-2	9	30.0 ± 10.1	8.5 ± 1.9	21.6 ± 10.3
PL-1	6	27.9 ± 12.5	8.4 ± 2.7	19.4 ± 10.2
PL-3	9	16.6 ± 7.1	6.9 ± 1.1	9.7 ± 6.6
EMR	7	27.9 ± 8.9	7.7 ± 1.4	20.2 ± 7.9
PRV	6	36.9 ± 11.8	8.2 ± 1.2	28.7 ± 10.6
All subjects	**57**	29.4 ± 11.2	8.4 ± 2.5	21.0 ± 10.4

*All calculator times are significantly less than standard method times at $P < .0067$; paired *t* tests. Values are mean ± SD.

†MS-3 indicates third-year medical student on first pediatric rotation; MS-4, fourth-year medical student on elective pediatric rotation; FP-2, second-year family practice resident; PL-1, first-year pediatric resident; PL-3, third-year pediatric resident; EMR, emergency medicine resident; and PRV, private practice pediatrician.

Table 2.—Accuracy Scores (% Correct, Range) by Method of Calculation*

Group†	No. of Subjects	Standard Method, %	Programmable Calculator, %
MS-3	10	72 (59-81)	98 (96-100)
MS-4	10	74 (56-89)	98 (96-100)
FP-2	9	80 (56-93)	99 (96-100)
PL-1	6	69 (59-81)	99 (96-100)
PL-3	9	77 (59-93)	96 (85-100)
EMR	7	71 (33-93)	97 (92-100)
PRV	6	65 (44-92)	99 (96-100)
All subjects	**57**	73 (33-93)	98 (85-100)

*All calculator scores show significantly more accuracy than standard method scores ($P < .0001$).

†MS-3 indicates third-year medical student on first pediatric rotation; MS-4, fourth-year medical student on elective pediatric rotation; FP-2, second-year family practice resident; PL-1, first-year pediatric resident; PL-3, third-year pediatric resident; EMR, emergency medicine resident; and PRV, private practice pediatrician.

Errors using traditional methods included mathematical errors, decimal point errors, erroneous fluid types, failure to designate fluid types, erroneous endotracheal tube size, erroneous pressor mixtures and infusion rates, and omitted answers. Many participants did not complete the problems for vasopressor mixtures and rates in the standard methods test. All of these errors would have been considered clinically significant. The only errors seen with the programmable calculator involved not designating fluid or insulin type in the diabetic ketoacidosis scenario and a single incorrect dopamine rate in the asystole scenario. These errors occurred because the subject incorrectly or incompletely transcribed the information supplied by the programmable calculator. No errors using the programmable calculator involved entering incorrect numbers.

COMMENT

This study highlights the difficulty that medical students, house staff, and attending physicians may have with drug and fluid management in pediatric emergencies. Even with the "open book" approach used for the standard method scenarios, erroneous calculations were frequent, and calculations took significantly longer compared with those made using the programmable calculator. These problems occurred in a simulated setting, without the pressures and distractions of procedures and medication administration that accompany a true emergency.

The significantly decreased time and improvement in accuracy of calculations seen with the use of the programmable calculator should be helpful in caring for ill children. This program not only calculates drug doses but also offers guidelines for the type of fluids, drugs, and endotracheal tube sizes for various pediatric problems. The rare error made using the programmable calculator could have been avoided with the use of a printer or by improving the graphic display in our program. Students and physicians at all levels of training were able to use the calculator readily after a brief instruction period. Although few subjects had extensive computer expertise, most were enthusiastic about using the programmable calculator in their medical practices.

From a medical education standpoint, the study produced several interesting observations during the testing period. When approached about volunteering as a subject for our study, many subjects were somewhat wary and reluctant. Although our testing was done anonymously and with reference materials, our subjects verbalized concern that they would be unable to do an adequate job. In the group of subjects who used the programmable calculator for the first half of testing, many verbalized frustration with the manual calculations required with the second set of scenarios; although not statistically significant, this group tended toward slightly longer times for the standard calculations than those who had used the standard method first. Many of the test subjects wanted to review the calculations after testing was completed and to check their manual calculations with the programmable calculator. The study prompted many questions from subjects on all levels regarding drug dose calculations specifically and patient care in general. The fact that students, residents, and staff using the programmable calculator could produce quick, accurate orders without a statistical difference regardless of training level is definitely an asset.

Others have also noted the usefulness of computers in medical education[5,6] and in emergency medicine.[4,7-9] Programmable calculators have been used by others for drug pharmacokinetics,[10-12] in calculating hyperalimentation and nutritional needs,[13] in anesthesia,[14] and in pediatrics.[15] This programmable calculator is inexpensive ($85), small enough to carry in a pocket or to attach to a clipboard, and has printer output available with a cordless infrared signal to a small roll-tape printer ($100). It offers an inexpensive compromise compared with a large microcomputer.

The programmable calculator was enthusiastically accepted by almost every subject. Routine use of such a calculator should result in more error-free, standardized fluid and drug therapy. Such a goal is especially difficult to accomplish when physicians staffing emergency departments differ greatly in their training and experience level. The ability of this program not only to calculate drug doses but also to provide types of drugs, intravenous fluids, and endotracheal tube sizes offers many applications to clinical pediatric and emergency medicine practices.

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Psychosocial Predictors of Maternal and Infant Health Among Adolescent Mothers

W. Thomas Boyce, MD; Elizabeth A. Chesterman; Marilyn A. Winkleby, PhD

• Past work suggests that stressful life events and social support are significantly associated with a broad range of child health outcomes. Such associations have remained, however, generally modest in magnitude, suggesting that stress and support may be only proxy measures for a deeper, more central aspect of childhood psychosocial experience. One aspect of young people's lives that could plausibly mediate the effects of stress and social support on health is the sense of stability and "permanence" in ongoing life experience. We developed a standardized psychometric instrument for measuring a "sense of permanence" and employed the measure in a prospective 1-year study of health outcomes among 89 adolescent mothers and their infants. Psychosocial and demographic factors were significantly predictive of maternal, but not infant, health outcomes, and the sense of permanence appeared to operate as a "final common pathway" in the influence of psychosocial variables on health and illness end points. Results of the study underscore the importance of continuity and stability in childhood and suggest that changes in an individual's sense of permanence may underlie the previously documented health effects of stressful life events and social support.

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Over the past two decades, a substantial body of work has evolved examining the association between psychosocial stressors and child health. Studies of acute and chronic stressors in the lives of children have demonstrated significant, but modest, associations between environmental stressors and childhood illness.[1,2] The generally low magnitude of such associations has been attributed, in part, to the countervailing effects of supportive and protective aspects of social experience that have often gone unmeasured in studies of stress and disease. When measured, positive features of the social environment, such as social support, have been shown to have significant beneficial effects on illness end points in diverse populations of children.[3-5]

The underlying biological mechanisms that may explain a relationship between psychosocial factors and health have been elucidated by new knowledge regarding the physiologic correlates of emotion and social experience. Data from a variety of animal and human studies suggest that both positive and negative aspects of psychosocial experience can affect physiologic response.[6-10] Stressors in laboratory and natural settings have been shown to influence hormone secretion,[8,10,11] cardiovascular measures such as blood pressure and heart rate,[12-15] and immunocompetence.[16-19] In addition, there is evidence that the salutary effects of social support may arise from an activation of central nervous system centers controlling affective and emotional experience.[20] Taken together, these and other studies suggest credible physiologic mechanisms that may underlie the epidemiologic observations of a connection between psychosocial processes and disease.

Despite the accumulation of significant findings, current work on psychosocial factors in child health has been impeded by the following two related problems: (1) the consistently low magnitude of reported associations, and (2) the lack of a coherent, unifying theory that could account for the diverse, and sometimes opposing, effects of psychosocial variables. One explanation for the failure of social factors to account for a greater share of the variance in childhood illness outcomes is the possibility that measures of stress and social support are only markers for a deeper, more central aspect of a child's psychosocial experience. We have proposed in past reports[21,22] that the effects of both stressful and protective social factors might be usefully viewed as acting on child health through their capacity to undermine or sustain a child's sense of permanence and continuity in ongoing life experience. We defined "a sense of permanence" as the belief or perception that certain central, valued elements of life experience are stable and enduring, and we developed a reliable and valid psychometric instrument to measure this construct using a self-report questionnaire.[21] Our previous work provided preliminary cross-sectional evidence that the sense of permanence was significantly related to neonatal complications and maternal affect in a population of unmarried, adolescent mothers.

Antonovsky[23,24] and Syme[25] have similarly proposed that stress and social support (as well as other social factors) exert their effects through underlying influences on an individual's sense of coherence or control. However, missing to date from such unifying theories is a *prospective* test of the hypothesized relationships. In this article, we report the results of a longitudinal prospective study of adolescent mothers and their infants during the year following delivery. The study examined the specific hypoth-

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From the Division of Behavioral and Developmental Pediatrics, University of California, San Francisco.

Reprint requests to Division of Behavioral and Developmental Pediatrics, University of California, A203, 400 Parnassus Ave, San Francisco, CA 94143 (Dr Boyce).

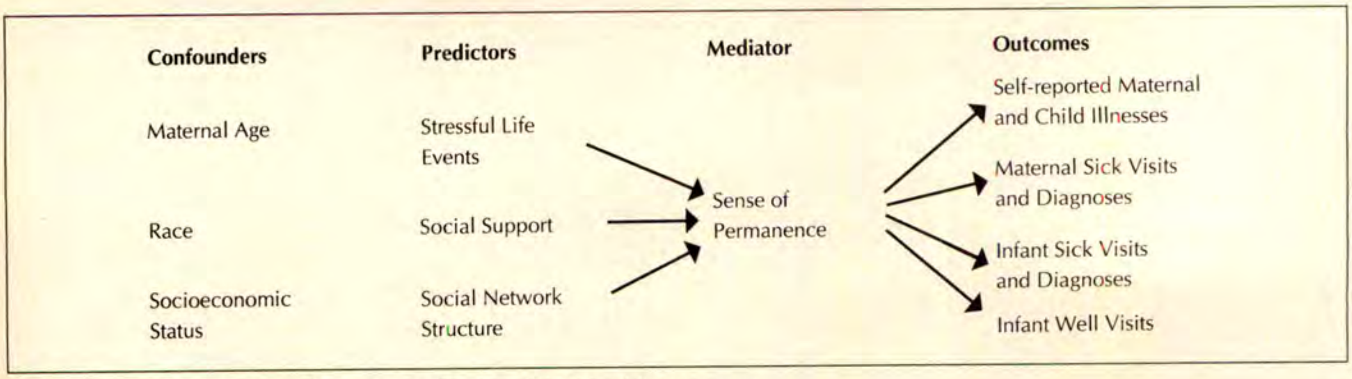

Fig 1.—*Theoretical model of effects on maternal and child health outcomes.*

esis that the effects of stressful and supportive experience on maternal and child health outcomes would be mediated, or accounted for, by underlying effects on the mother's sense of permanence.

SUBJECTS AND METHODS

A sample of convenience comprising 89 unmarried pregnant adolescents was recruited in Pima County, Arizona, from a variety of settings including schools, teenage-parent programs, clinics, and hospitals. All subjects were younger than 19 years, spoke English, and planned to retain primary responsibility for their babies' care following delivery. Subjects were offered free pediatric care for themselves and their infants during the 1-year study period as an incentive to enrollment. All subjects were recruited in their third trimester of pregnancy, and none who were approached regarding enrollment in the study refused to participate.

Figure 1 displays the independent and outcome variables assessed, the timing of variable measurements, and the theoretical ordering of their hypothesized relationships. Age, race, and socioeconomic status (SES) were viewed as potential confounders and are listed in the first tier of variables as factors to be controlled for in testing the principal study hypotheses. Stressful life events, social support, and social network structure were viewed as predictor variables and are shown in the second tier of the causal chain. All six of the variables in the first two tiers were assessed as baseline measures in the perinatal period, within 2 weeks before or after delivery. Sense of permanence was regarded as a more distal mediator variable and was measured in the fourth postpartum month. The outcome variables—self-reported maternal and infant illnesses, maternal/infant "sick visits" and diagnoses, and infant "well visits"—were assessed prospectively from the fifth through the 12th postpartum months using biweekly completion of home health diaries and medical record reviews. It is important to note that one of the study's methodologic strengths was the prospective, sequential measurement of variables, which replicated the theoretical ordering of the hypothesized causal relationships. Age, race, SES, stressful life events, social support, and social network structure were thus viewed as causally antecedent to a sense of permanence and were measured prior to the assessment of sense of permanence. Sense of permanence, in turn, was regarded as antecedent to the health outcomes and was measured in the month prior to the prospective collection of outcome data.

Based on subject response, race was coded as black, white, Hispanic, or Native American. Socioeconomic status was scored using a modification of Green's index[26] of social position, which was based on the income of the household in which the subject lived and the occupation of the main wage earner.

Stressful life events were assessed for the 4-month period preceding delivery using a set of 50 life event items compiled from the studies by Coddington,[27] Holmes and Rahe,[28] and Monaghan et al.[29] Previous work with life event instruments[30,31] has confirmed strong reliability and validity characteristics and has suggested that consensus weightings of events account for little, if any, additional variance in health outcomes. Because of this, scores in this study were calculated as the simple, unweighted frequency of reported life events.

Social network structure and social support were measured using an instrument drawn from the work of Berkman and Syme[32] and others.[33-35] Consistent with current work distinguishing structural and functional aspects of social affiliation,[36] two measures were employed: one describing and counting existing social ties and the other ascertaining the degree to which members of the social network served particular supportive functions. Social network was operationally defined as those relatives and friends with whom subjects made planned contacts at a frequency of once or more per month. The measure of social network structure was scored as a sum based on the following: (1) marital status (0, unmarried; 1, married to person other than infant's father; 2, married to infant's father), (2) the number of network members (0 to 2, lowest three deciles on social network size; 3, all others), and (3) the subject's relationship to the person(s) with whom she was living (0, alone or with other adults; 1, subject's parents or infant's father). Social support was defined as benefits derived from interactions with network members and was scored based on functional questions regarding the provision of favors and assistance by individuals (equally weighted subscores for "special favors," "gone out of the way to help," "discussed personal problem," and "really count on").

Sense of permanence was assessed using a previously reported 40-item scale.[21] Items were generated to reflect perceptions and experiences theoretically consistent with a sense of permanence. These included (1) an awareness of *self* as reliable and consistent, (2) the perception of stability in important interpersonal *relationships*, (3) the identification of certain *places* as special points of reference, (4) the awareness of behavioral patterns and *routines* in day-to-day activities, and (5) a consciousness of religious or *spiritual principles* that suggest a universal order. Five of the original 40 items had insufficient variation in responses and were excluded. Factor analysis was applied to the remaining 35 items, and the 19 items that loaded together in the first factor were used as the final measure of sense of permanence (Table 1). Assessment of the measure's reliability demonstrated high internal consistency with Cronbach $\alpha = .81$. (In the only previous use of the instrument measuring sense of permanence, 277 randomly selected men and women ranging in age from 15 to 92 years were administered the questionnaire in two family medicine clinics. There were no significant age or sex differences in scores, and the internal consistency of the scale [Cronbach $\alpha = .84$] was as high as that found in our study.)

As noted above, self-reported maternal and infant illnesses were measured using a home health diary that was completed every 2 weeks from the fifth through the 12th postpartum month. Diaries included reports on symptoms of illness for both mother and infant, number of sick days in the 2-week period, and general well-being on a 10-point Likert scale. Maternal and infant sick visits, maternal and infant diagnoses, and infant well visits were compiled from medical record reviews. Since free medical care was provided to the mothers and their infants, a large majority of the care was given at a single site, the Pediatric Clinic at the University of Arizona Health Sciences Center, Tucson. Emergency department and weekend care was occasionally sought at other sites. In every known case, however, visits outside the university clinic were reported to study personnel by the subject,

Table 1.—Sense of Permanence Scale*

Score	Statements Describing People's Feelings About Themselves, the World, and People Closest to Them
+1	I feel sure of my family's love for me
+2	I have friends I can really count on
+3	Despite all the problems in the world, I feel pretty hopeful about life
+4	I am a fairly stable person
−5	My family is sometimes inconsistent in the way they respond to the things I do
−6	My relationship to my family feels pretty uncertain some of the time
−7	It does not take much to upset me
−8	Nothing is very permanent
−9	My friendships tend to come and go
+10	I have great faith in the person who is closest to me
−11	Sometimes I really think the world is falling apart
−12	I am not always sure where I stand in my closest relationship
+13	I feel pretty settled in my home right now
−14	I do not feel very connected to any special place right now
−15	Even the person you are closest to cannot always be counted on
−16	Sometimes it seems like everything is changing too fast around here
−17	My reactions to new situations are fairly unpredictable
−18	I am never really sure how some of my friends feel about me
−19	Something always interrupts the routines I try to follow

*To compute sense of permanence score, a score of 1 is assigned to each positive item circled and 1 to each negative item *not* circled. A score of 0 is assigned to the remaining items. Then the sum of item scores is added for the total score. Pluses and minuses were not included in subject's version.

Table 2.—Frequency Distributions for Independent and Outcome Variables

Variable	Mean ± SD	Range
Maternal age, y	16.5 ± 1.2	14-18
Maternal race*	. . .	. . .
Socioeconomic status	101.7 ± 17.0	58-141
Stressful life events	17.6 ± 6.3	7-33
Social support	29.2 ± 14.5	5-77
Social network structure	3.0 ± 1.1	0-4
Sense of permanence	11.6 ± 4.2	3-19
Maternal days sick†	10.6 ± 8.1	0-45
Infant days sick†	18.2 ± 8.3	1-37
Maternal symptoms†	42.1 ± 20.5	10-122
Infant symptoms†	67.9 ± 20.4	20-120
General well-being†	100.5 ± 22.5	34-143
Maternal sick visits†	1.2 ± 2.2	0-12
Maternal diagnoses†	1.5 ± 2.1	0-12
Infant sick visits†	3.8 ± 3.9	0-17
Infant diagnoses†	4.5 ± 3.8	0-17
Infant well visits†	2.4 ± 1.1	0-5

*Forty-three percent were white, 37% Hispanic, 18% black, and 2% Native American.

†Principal-components analysis of these 10 variables identified four factors that served as the outcome variables for the subsequent test of study hypotheses. For each factor, scores on component variables were standardized and summed to derive the outcome variable score. The four outcomes were designated self-reported maternal and infant illnesses; maternal sick visits and diagnoses; infant sick visits and diagnoses; and infant well visits.

thereby allowing review of all medical records and a comprehensive summary of medical care utilization. All outcome data were gathered by study personnel who had no knowledge of subjects' prior responses on measures of independent variables.

Statistical analyses first examined frequency distributions for independent and outcome measures and Pearson correlation coefficients for the bivariate relationships among pairs of variables. The hypothesized relationships depicted in Fig 1 were tested with path analysis using a series of standard multiple regression equations.[37] In this path analytic approach, each variable in the second through the fourth tiers in the causal model was regressed on all antecedent variables. Stressful life events were therefore regressed on maternal age, race, and SES; sense of permanence was regressed on all six of the variables in the first and second tiers, and so on. The resultant path model provided a summary estimate of the degree to which data conformed to Fig 1, the hypothesized set of causal associations.

RESULTS

Table 2 presents the frequency distributions for all independent and outcome variables. The mean age of study subjects was 16.5 years, with a range of 14 to 18 years. The distribution of the study population by race was 18% black, 43% white, 37% Hispanic, and 2% Native American. These distributions were comparable with those of the Pima County population of adolescent mothers from which the sample was drawn, except that mothers younger than 15 years were slightly overrepresented (7% vs 3%) and Native American mothers were underrepresented (2% vs 17%).[21] Socioeconomic status had a broad and representative range.

The average number of life events reported in the perinatal period was 18, reflecting the tumult and change that often accompany a teenage pregnancy and birth. Among the events most frequently reported were "change to a different school," "change in the way friends treat me," "not making it into an extracurricular activity I wanted to be involved in (ie, athletic team, band, etc)," "change in my financial situation," and "move to a new house or apartment." The measures of functional and structural social support, as well as the sense of permanence score, showed extensive variability around generally normal distributions.

Table 2 also displays the frequency distributions for component variables within the four outcome measures. Over the 8-month follow-up period between the infant's fifth and 12th month of life, mothers reported an average of 11 sick days for themselves and 18 sick days for their infants. These periods of illness resulted in a mean of 1.2 physician visits for mothers and 3.8 visits for infants, indicating as expected that an infant illness was more likely to result in a medical visit than a maternal illness. The number of well child visits over the first year of life—an index of maternal use of preventive pediatric care—averaged only 2.4, a number substantially below the five or six well child visits generally recommended.

Not shown in Table 2 is the finding that correlations between serial measures of the sense of permanence over approximately 4-month intervals averaged about 0.70. It is consistent with our theoretical view of this construct that the correlations demonstrate a reasonably high level of temporal stability, but a significant influence of changing life circumstances as well.

Initial analysis of bivariate relationships among pairs of independent variables (ie, confounders, predictors, and mediator) and outcome variables revealed several significant findings. The tabulation below displays correlation

Table 3.—Bivariate Relationships Among Psychosocial Variables and Maternal and Infant Health Outcomes (Pearson Correlation Coefficients)

Psychosocial Variables	Self-reported Maternal and Infant Illnesses	Maternal Sick Visits and Diagnoses	Infant Sick Visits and Diagnoses	Infant Well Visits
Stressful life events	.39*	.27*	.06	−.01
Social support	−.14	−.04	−.09	.10
Social network structure	−.21†	−.09	−.02	.09
Sense of permanence	−.44*	−.24†	.01	.14

*$P<.01$.
†$P<.05$.

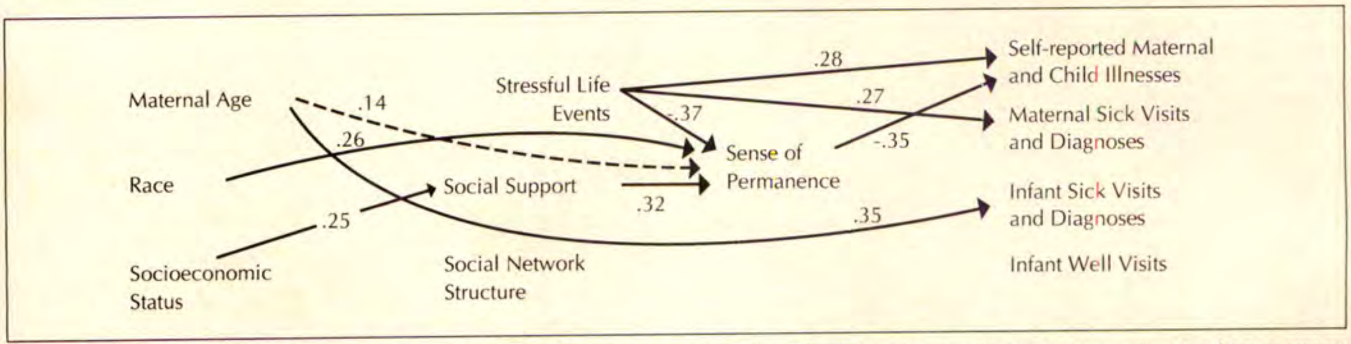

Fig 2.—*Path model of effects on maternal and child health outcomes.* $P\leq.01$ *for all solid paths;* $P<.10$ *for broken path. Numbers represent standardized regression coefficients.*

coefficients for the associations found between predictor variables and the score of sense of permanence.

Predictor Variables	**Sense of Permanence Score, Pearson *r* (*P*)**
Stressful life events	.31 (<.01)
Social support	.29 (<.01)
Social network structure	.23 (<.05)

As predicted by our theoretical model, higher sense of permanence was significantly related to fewer stressful life events, higher perceived social support, and a larger social network structure.

Table 3 shows bivariate associations among predictor, mediator, and outcome variables. Stressful life events were significantly related to self-reported maternal and infant illnesses and to maternal sick visits and diagnoses, with higher numbers of events associated with higher levels of each of these illness outcomes. Perceived social support was unrelated to any outcome, and network structure was associated only with self-reported illnesses. Sense of permanence, on the other hand, was significantly related both to self-reported illnesses and to maternal sick visits and diagnoses. The strongest of all examined bivariate relationships was the inverse association between sense of permanence and self-reported maternal and infant illnesses, indicating that subjects with a high sense of permanence reported fewer illnesses for both themselves and their infants ($r=-.44$, $P<.01$).

It is important to note that the only significant bivariate associations with psychosocial variables were those found for outcomes based on *maternal* rather than infant data. Five of eight correlations with maternal outcomes were significant, whereas none of eight with infant outcomes reached significance. Stressful life events and sense of permanence were significantly related only to self-reported illnesses (a variable based on the mother's perceptions) and maternal sick visits and diagnoses (a variable based on the mother's clinical illness experience). Examination of bivariate associations thus offered preliminary support for the proposed theoretical model (Fig 1), but only for end points derived from *maternal* perceptions and experiences.

Multivariate analyses were required to test hypotheses regarding causal ordering and to assess the independent effects of predictor and mediator variables while controlling for the potential confounding effects of maternal age, race, and SES. Figure 2 displays path analysis data derived from the three sequential multiple regression procedures corresponding to the variables in the second, third, and fourth tiers of the theoretical model. Only significant or borderline significant paths identified by the regression models are displayed. Maternal age, race, and SES were significantly related to various predictor, mediator, and outcome variables. Maternal age, for example, was strongly associated with infant sick visits and diagnoses such that older maternal age was predictive of more infant sick visits and diagnoses. Stressful life events were related to sense of permanence and two of the outcome variables, self-reported illnesses and maternal sick visits and diagnoses.

Sense of permanence appeared to operate as the final common pathway for a number of antecedent confounder and predictor variables, including maternal age, race, stressful life events, and perceived support. Each of these variables was predictive of self-reported maternal and infant illnesses, but *through* their influence on the mother's sense of permanence. Sense of permanence scores remained strongly and inversely associated with self-reported illnesses, even after adjustment for the effects of demographic and other psychosocial measures. It is again important to note that, although the sense of permanence and other psychosocial variables were strongly related to health outcomes, the significant relationships found in this regression model were almost exclusively those with end points derived from maternal, rather than infant, experience.

COMMENT

This study confirmed, in part, the hypothesized relationships of psychosocial factors to health outcomes over the first year following an adolescent pregnancy. The data presented provide evidence that (1) an adolescent mother's stressful and supportive social experience is a significant prospective predictor of maternal health outcomes during the first year of her infant's life; (2) a young mother's sense of permanence, defined as her perception of stable continuous aspects of ongoing life experience, is significantly determined by demographic factors, such as her age and race, and by psychosocial factors, such as stressful events and social support; and (3) psychosocial factors have both direct and indirect effects on maternal health outcomes, with indirect effects operating *through* the young woman's sense of permanence.

While not all aspects of our theoretical model were confirmed by these data, several important elements of the model were strongly supported. Results of the path analysis indicate, for example, that virtually all demographic and psychosocial variables affected the young mother's sense of permanence, and the influence of these variables on health outcomes operated almost entirely through intervening effects on the sense of permanence. Furthermore, the strongest association found in the study was the inverse relationship between scores of sense of permanence and self-reported illnesses, so that subjects with a weaker sense of permanence recorded significantly higher rates of illness for both themselves and their babies. Note that it is impossible, using these data, to disentangle actual maternal and infant illness experience from the mother's *perception* of illness events. Nonetheless, the findings support the general conclusion that a young mother's sense of permanence and stability exert significant influences on her illness experience, her subjective appraisal of illness symptoms, or both.

Several aspects of the proposed theoretical model were *not* confirmed, however, by data derived from the study. In particular, predicted relationships were not found between the sense of permanence and the more objective, medically based measures of sick visits and diagnoses. The bivariate association, for example, between scores of sense of permanence and maternal sick visits and diagnoses did not reach significance after adjustment for the effects of confounder and predictor variables. Further, no significant associations were found between psychosocial variables and infant, as opposed to maternal, health outcomes. The only significant relationship with infant outcomes was that noted between maternal age and infant sick visits and diagnoses. Taken together, these findings indicate that, in the setting of adolescent pregnancy and parenthood, the sense of permanence and other psychosocial factors may have stronger effects on maternal than on infant outcomes and be more highly correlated with self-reported appraisals of health status.

Several shortcomings in the design of the study and in the character of the data should be taken into account in evaluating the reported findings. First, the study sample is relatively small and was not chosen at random from a larger population of adolescent mothers. Inspection of the sample's demographic characteristics nevertheless indicates moderate comparability with the population of teenage mothers in Pima County, where subjects were recruited. Second, three of the psychosocial variables employed in the study—social support, social network structure, and sense of permanence—were assessed using instruments designed for this study, on which only limited psychometric information is currently available. The reliability of the measure of sense of permanence is supported by the findings of strong internal homogeneity and high stability over time. Construct validity of the measure is undergirded by the significant associations found, in the expected direction, between sense of permanence and both stressful life events and social support. Finally, the finding that sense of permanence was related only to *self-reported* health status and not to more objective measures of medically generated diagnoses raises the issue of a "response-set," which could create spurious associations among subjective, self-report measures. There is thus the possibility that some characterologic feature of certain subjects could create a tendency to underestimate experiences of stability and continuity and to overestimate experiences of illness. Such a process occurring in a subset of subjects could potentially result in a biased association between the sense of permanence and self-appraised health status.

On the other hand, past independent observations and research findings similarly suggest the importance of a child's experiences of continuity and stability. Developmental theory, for example, has emphasized the significance of object relations in early childhood and the child's "search for constancy" in the establishing of social bonds. Bank and Kahn[38] wrote that "A young child needs a stable, reliable environment or 'object constancy' . . . the child who can fuse or merge with another person will feel more whole, more integrated, and less vulnerable to the vagaries of an uncertain world."

Similarly, Erikson[39] suggested that the development of "basic trust" in the first year of life depends, in part, on "an outer predictability (the mother) becoming an inner certainty," the process by which the infant maps parental dependability onto the larger arena of ongoing life experience. Others[40,41] have noted children's use of treasured transitional objects from infancy to adolescence as another source of familiarity and a symbol of constancy during moments of fear, discomfort, or difficult change.

Even in adult life, the stable presence of other persons can be a meaningful source of comfort and solace during times of stress. Kennell et al,[42] for example, found that for pregnant women the presence of a supportive companion during labor resulted in a significant decrease in the need for medical interventions such as cesarean or forceps deliveries or epidural anesthesia. Medical and biological effects of a supportive social environment have become increasingly well known,[36] but what is remarkable about the study by Kennell et al is that much of the protective effect persisted when the labor companion *only observed* without interacting with the mother. This finding suggests that simply the stability and continuity inherent in having another person in the room throughout labor was itself a protective social factor.

In work suggesting the relevance of an even more mundane aspect of social experience, Boyce and colleagues[43,44] have demonstrated that family rituals and routines can provide children with a stable point of reference during times of unsettling change in the life of the family. In one study, respiratory illnesses among preschool children were more prolonged and more severe in children whose families had fewer and less predictable routines. The notion that ritual behavior may have important influences on health has been further advanced by the work of Ehlers et al,[45] indicating that disruption of social rhythms may result in unstable biological rhythms and trigger the onset of major depressive episodes in adult subjects. It is important to note in these studies that the presence of rituals and routines is one component of the sense of permanence construct.

Related to the experience of routines, predictability appears to be a salient central dimension of social experience during times of major stress. The animal study by Weiss[46] demonstrated that unpredictable shock was many times more pathogenic than predictable shock of equal intensity in producing gastrointestinal lesions in laboratory animals. Similarly, Seligman[47] has shown that inescapable, uncontrollable shock results in a state of helplessness and slow learning that mimics clinical depression. In their work with chronically ill children, Jessop and Stein[48] have pointed out the importance of uncertainty and unpredictability in patients' experiences of illness. Further, Mechanic's[49] study of illness behavior in adolescence indicates that discontinuities in family life and social experience tend to exacerbate the perception of bodily symptoms, while stability and predictability tend to protect against preoccupation with self-perceived symptoms.

Finally, paralleling our proposal here, a number of other investigators have proposed that a central, underlying construct might account for the health effects of diverse psychosocial factors such as life events, social support, or styles of coping. Our theoretical frame of reference and research findings are highly convergent, for example, with the work of Antonovsky[23,24] on the "sense of coherence." Citing a variety of evidence, he proposes that underlying an individual's capacity to resist disease is a "way of seeing the world," a perception of life experiences as predictable, understandable, and ordered. Rodin,[50] in addition, sees the individual's "sense of control" as the central psychological attribute determining health and resilience, and Syme[25] has proposed that one's "control of destiny" is perhaps the most salient aspect of health-altering psychosocial experience.

In conclusion, we have offered a perspective in which the various effects of psychosocial factors in *childhood* are seen as operating through the child's evolving belief in the stability and continuity of life experience. For a contemporary child, the already tumultuous changes inherent in growth and maturation are magnified by a set of powerful societal forces that include divorce, poverty, residential mobility, family isolation, violence, and a host of others. It is our hope, in presenting the data reviewed above, to underscore for those who care for the health of children the critical importance of permanence and stability in the lives of the patients they treat.

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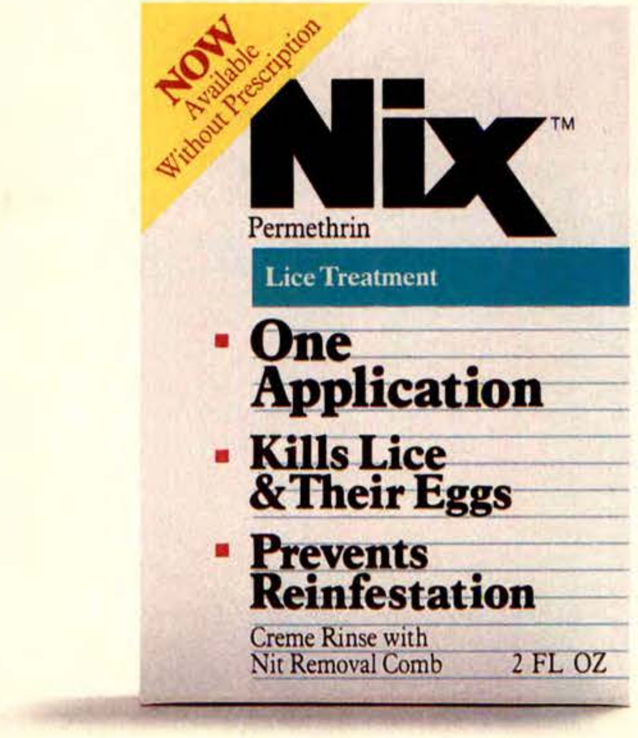

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Photographing the Physically Abused Child

Principles and Practice

Lawrence R. Ricci, MD

• **Photographic documentation of significant findings is an important part of any child abuse evaluation. High-quality photographs of significant physical findings may be important in helping courts to adjudicate whether child abuse has taken place. The physician evaluating abused children should ensure adequate photographic documentation of visible lesions. Physicians who care for abused children should be familiar with the basic principles and techniques of clinical photography. These include good equipment, adequate lighting, and planned composition. Equally important is a working knowledge of camera equipment, film procedure, and medicolegal implications. This review outlines for the practicing physician the basic concepts and techniques of photographing abused children.**

(*AJDC.* 1991;145:275-281)

Photographic documentation of significant findings is an important part of any child abuse evaluation.[1-6] The American Medical Association's diagnostic and treatment guidelines for the abused child recommend that all visible lesions be photographed.[2] High-quality photographs of significant physical findings may be important in helping courts to adjudicate whether child abuse has taken place.[7]

See also pp 255 and 256.

This review outlines for the practicing physician the basic concepts and techniques of photographing abused children. The focus of the review will be on the physically abused child; however, the principles apply equally to the sexually abused child. A detailed review of photographing sexually abused children is presented elsewhere.[5] Although some institutions have access to professional photographic staff either inside the institution via a media department or outside via law enforcement, many do not.[1] It is incumbent on physicians evaluating abused children to ensure adequate photographic documentation of visible lesions either by taking the photographs themselves or by guaranteeing that they are taken by someone else. Indeed, many states require that reasonable efforts be made by the reporting hospital staff member to take or cause to be taken color photographs of any areas of visible trauma on the child.[1] Every physician who cares for abused children should be familiar with the basic principles and techniques of clinical photography.

These principles include good equipment, adequate lighting, and planned composition. The key equipment concerns are camera, lens, lighting, and film. A high-quality lens, adequate flash, and proper technique are of far greater importance than the brand or features of a camera.[8] No particular system is best. Decisions should be based on the needs of the photographer and the cost of the system.

CAMERAS

Camera systems recommended for photographing the abused victim range from expensive and sophisticated 35-mm close-up systems[5,6,9-11] to less expensive and simpler instant or self-developing camera systems.[3] Although new technologies, including videotape and computer-based digital image manipulation, are emerging, 35-mm slide and print photography remains the standard for patient documentation.[12]

Specific camera types available include instant-processing cameras, fixed-focus lens "point and shoot" 35-mm cameras, traditional 35-mm single lens reflex (SLR) cameras, and "bridge" cameras, a new generation of 35-mm cameras offering the simplicity of a fixed-focus lens camera and the versatility of a 35-mm SLR camera.

Instant-processing cameras have the advantage of simple operation and low initial cost. Their disadvantages include poor resolution and poor color rendition compared with 35-mm cameras and film.[1] This is particularly a problem when photographing subtle or faded bruises. Instant-processing cameras also have minimal close-up capability and require expensive film that is difficult to reproduce and store. The best argument for using an instant-processing camera is that the print develops just after the photograph is taken, guaranteeing at least some form of documentation. One compromise, particularly when there is a need for immediate documentation, is to take both instant and 35-mm photographs.

Fixed-focus lens "point and shoot" 35-mm cameras are inexpensive and easy to use, yet, much like instant-processing cameras, in the past they have offered limited close-up capability and expandability. Newer "point and shoot" cameras, however, have a variable focal length and often a modicum of macro capability (see below, the section on "bridge" cameras).

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Serious medical photography requires a camera that offers control over aperture, focusing, and shutter speed. The camera should also be able to accept a variety of lenses and other attachments. The 35-mm format offers an unrivaled choice of cameras, lenses, and accessories and, hence, excellent close-up capability and resolution. The most widely used 35-mm camera is the 35-mm SLR camera. A reflex camera is one whose viewing system employs a mirror to reflect the image onto the viewing screen. The mirror swings out of the way to expose the film when the shutter is released. A 35-mm SLR camera uses 35-mm film and a single lens for both viewing and recording the image. The photographer sees the same image as the lens and the film; this is important when using close-up or zoom lenses.

The most versatile system for the relatively skilled photographer utilizes a 35-mm SLR camera body with a series of lenses (eg, 50-mm, 105-mm, 35- to 105-mm zoom, and macro lenses) and both hotshoe and ring flashes.[5] The accessories may be used in various combinations depending on the clinical circumstances. Combining a 35- to 105-mm zoom lens with a 105-mm macro lens offers the most versatility. Attached to a 35-mm camera, a macro lens or a standard lens with close-up adapters allows photographs of fine anatomic detail otherwise not easily documented.[5] A colposcope mount may be useful for magnifications greater than life size, particularly of the genitalia.[6] Although adaptable to most clinical photographic situations, a traditional 35-mm SLR camera may be expensive and technically demanding.

The simplest system for a multiuser environment or for those unable to master a 35-mm SLR camera is a so-called "bridge" camera. These cameras combine the simplicity and ease of use of (bridge the gap between) a point and shoot camera with the versatility, expandability, and close-up capability of a 35-mm SLR camera.

LENSES

Lens quality, more than anything else, determines picture quality. Lenses come in three basic types: normal focal length, wide angle, and long or telephoto. The description of a particular focal length is dictated by the format (negative or transparency image size) of the camera. A normal lens is one in which the focal length approximately equals the diagonal measurement of the camera film format. For a 35-mm camera, a normal focal length would be 50 to 55 mm. A wide-angle lens would be 28 to 35 mm, while a long lens would be 80 mm or greater. Thirty-five–millimeter film is supplied in sprocketed rolls of variable length depending on the number of photographs on the roll. In all cases the width of the film on the roll is 35 mm. The image on the film, however, is 24×36 mm. The diagonal of the image size determines the lens classification.

The ideal lens for medical photography should have good optics, medium telephoto focal length (85 to 105 mm) to minimize distortion, and macro or close-up capability up to ×1 (the image on the negative or transparency is magnified to life size).

Magnification is the ratio of image size on the negative or transparency to actual object size (m = image size/object size). It can be expressed as a ratio (1:2), a fraction (1/2), a decimal (×0.5), or a percentage (50%). Close-up magnification is ×0.1 to ×0.5, extreme close-up magnification is ×0.5 to ×1, and true macro magnification is ×1 to ×35. For example, photographing an 8-year-old child using a 35-mm format would produce the following views on the print or slide at different magnifications: ×0.05, full body; ×0.1, half body; ×0.2, face or hand; ×0.5, ear, lips, and eye; and ×1, fingernail or hymen.

The maximum magnification of a lens can be checked by focusing the camera on a metric ruler at the closest focusing distance of the lens. With a 35-mm SLR camera, the viewfinder screen and film are both 36 mm wide. Thus, if the screen or the film "sees" a 36-mm segment of ruler horizontally (at the closest working distance of the lens), the magnification is ×1. If the screen sees 72 mm, the magnification is ×0.5 (m = 36 mm/No. of millimeters "seen" horizontally on the viewfinder screen).

The lens focal length dictates lens-to-subject distance, which in turn determines image distortion. A 90- to 110-mm lens is recommended for close-up work, particularly facial work, when using a 35-mm camera.[13] Long lenses compress or flatten perspective. This flattening is advantageous in face shots, because features such as the nose are less distorted. For torso or full-length photography, a 50- or 55-mm lens is adequate.[12] In general, a medium telephoto lens, such as a 105-mm lens, is best for everything from ×0.2 to ×1 (from the head and neck down to the fingernails), while a wider (55-mm) lens should be used for full- and half-body length photographs only (×0.05 to ×0.1).[1,14]

An additional advantage of a longer focal length is greater working distance. A typical 50-mm lens at a magnification of ×0.1 has a close working distance of 25 cm. A 100-mm lens doubles this working distance. Children may be less fearful if the camera is further away, ie, if the subject-to-lens distance is increased. In addition, flash illumination is more uniform as the distance increases.[11]

For very close work, magnifications greater than ×0.5, a macro lens provides the best solution. A macro lens is one capable of providing a magnification of ×1 or greater, although the term *macro* is often used to describe any close-focusing lens. Lenses sold as "zoom with macro focusing" are not true macro lenses and often magnify only up to ×0.25. True macro lenses have their barrels embossed with magnifications, especially from ×0.5 to ×1.[15]

A relatively inexpensive alternative to a macro lens for close-up work is a set of close-up or supplementary lenses. These are lens attachments placed over the normal lens to magnify the image. These auxiliary lenses provide magnification up to ×0.5. However, using close-up lens attachments to achieve magnifications greater than ×0.5 significantly reduces image quality. Beyond ×0.5, a macro lens offers the best option. Bellows and extension tubes, although cumbersome and difficult to use, are another option. Colposcopic camera attachments use the extension-tube principle to achieve magnifications of ×1 or greater.

Zoom lenses offer variable focal length. This allows one lens to be used for both close-up and distant work. By changing the focal length, zoom lenses allow the photographer to remain stationary while changing the magnification. Some zoom lenses provide macro capability up to ×0.25.

A particular problem in close-up work is narrow depth of field. Depth of field is the zone of acceptable sharpness extending in front of and behind the center of focus. It is determined by aperture, lens focal length, and subject-to-lens distance. The aperture or opening within the lens that limits the amount of light reaching the film can be varied by means of a diaphragm. The opening is measured by an f-number. The larger the aperture (ie, the smaller the f-number), the narrower the depth of field. In the close-up range, depth of field can be quite narrow (a typical 105-mm macro lens focusing at ×1 magnification at f-22 has a maximum depth of field of 4 to 6 mm). This can particularly be a problem with deep cavities, such as the rectum, where the pathology may have a greater depth than the depth of field of the camera. This problem may necessitate a series of photographs, each focused at different points near and far, none of which captures the entire area. When depth of field is a problem it is important not only to focus carefully but also to try to position the subject and/or the camera so that all of the important parts to be photographed fall in a plane parallel to the film. A powerful flash can improve depth of field by allowing a smaller aperture.

LIGHTING

Lighting is the single aspect that most directly affects the quality and usefulness of a medicolegal photograph. Proper lighting can show texture, color, depth, and contours. Improper lighting can hide details in shadow, wash out bruises, and even misrepresent evidence.[1,14,15]

Short of three-source studio lighting, electronic flash offers the best light for indoor color medical photography.[12,15] There are two basic types of electronic flash units, a traditional point-source flash mounted to one side or on top of the camera and a ring flash that encircles the camera lens.

A ring flash provides the best overall lighting in the form of shadowless, uniform illumination. This is particularly useful when photographing cavities and recesses, such as the mouth, vagina, and rectum. Shadowing for detail, important in black-and-white photography, is less important when using color film, which utilizes varying colors and hues to separate detail.

With modern through-the-lens (TTL) metering systems, flash use has become quite simple. The flash may be connected to the shutter for synchronization either through a coaxial cable or directly through a shoe fitting on the camera (hotshoe). Many electronic flash guns have automatic exposure control. Light from the flash is reflected from the subject back to a sensing cell. When sufficient light has been reflected, the cell cuts off the current and the light is switched off. The light-producing power of a flash is measured by its guide number (for a given film speed the guide number equals the f-number chosen multiplied by the lens-to-subject distance). A higher guide number represents a more powerful flash. A more powerful flash allows a smaller aperture and, hence, a greater depth of field.

Limitations of electronic flash include reflections, particularly from mucous membranes; loss of three-dimensional quality of textured areas, such as abrasions; washout of subtle colors by overexposure; and inadequate lighting, especially if the flash is blocked by the lens.[1,14] When using an electronic flash, it is important to remove or neutralize other light sources, such as shadow-producing operative lights or sunlight, which may only illuminate a portion of the subject and create exposure imbalance.

Flash recycle time, the time it takes the flash capacitor to recharge and be ready to fire again, is especially important when photographing children. The difference between 3 to 5 seconds and 20 to 30 seconds may be the difference between a good photograph and none at all with a child who is unwilling to sit still for the several seconds it takes a slow flash to recycle. As batteries discharge, recycle time lengthens; thus, fresh batteries should always be used.

FILM

Thirty-five–millimeter color slide film, sometimes called color transparency or color reversal film, remains the standard for medical use.[12,15] Color film offers a distinct advantage over black-and-white film, in that color film uses the various hues of the subject to separate details much more effectively than shades of grey.[1] Color slides are relatively inexpensive, quickly developed, and easy to file and can be converted into satisfactory color prints if necessary.[12,15] Although color negative or print film offers greater exposure and contrast latitude and, hence, is more forgiving of exposure mistakes, color slide film offers a distinct advantage by providing a first-generation image that can be projected. Because color negative film necessitates a second-generation conversion into a print, the color balance may be distorted. Conversion of color negatives to slides also usually results in loss of sharpness and color balance.

Table 1.—Photography Shooting Tips

Table 1.—Photography Shooting Tips
Take a photograph with landmarks and one close-up of the lesion alone
Magnify in the original, not in a blowup
Arrange the subject so the surface of interest is parallel to film
Take several shots from different angles and distances
Compose the picture the way you normally look at the area
Keep the photographer and subject at the same level
Bracket shots if the correct exposure is uncertain
Shoot more slides rather than planning to duplicate
Shoot a face to identify the patient
Take a photograph of the patient's name
Use an uncluttered, neutral-colored background
Shoot only one patient per roll

Duplicating slides or prints may significantly alter color and resolution and should be avoided if at all possible.[1] Rather, two or three sets of slides should be shot initially, ie, each view should be photographed twice. One set can be used in court, while the others are retained with the child's record. Also, magnification should be accomplished in the original photograph by varying camera distance and/or focal length, not in the print- or slide-making process. As a rule, only one patient should be photographed on each roll of film. Even if a roll has only a few exposures, it should be developed rather than kept in the camera, where a mistake might either expose the film or lead to a mix-up of subjects.

Film speed is the sensitivity of the film emulsion to light, as measured by the International Standards Organization (ISO) rating. A film rated at 400 ISO is twice as light-sensitive or "fast" as one rated at 200 ISO. Slower film (with a lower ISO rating) offers a finer grain, which means greater sharpness and definition. However, slower film requires more light, a larger aperture, and, hence, narrower depth of field. Film should be fast enough to provide an aperture of f-11 or f-16. Medium-speed (100 ISO) daylight film allows a smaller aperture for greater depth of field yet minimum grain.[15] This is particularly true if a powerful flash is used.

A flash should always be used when shooting indoors with daylight film. Daylight film is color film balanced to give accurate color rendition in average daylight. The color temperature of daylight is 5000°K. Normal indoor lighting has a color temperature of 3000°K and will create significant color distortion if daylight film is used without a flash. Electronic flash is standardized to the same color temperature as average daylight.[16] A standardized color bar, although awkward, may be placed in the photographic plane for comparison with the subject color. However, if color is a significant concern, as when trying to age a bruise, it is far more useful to carefully document the coloring in writing than to rely on the photograph.

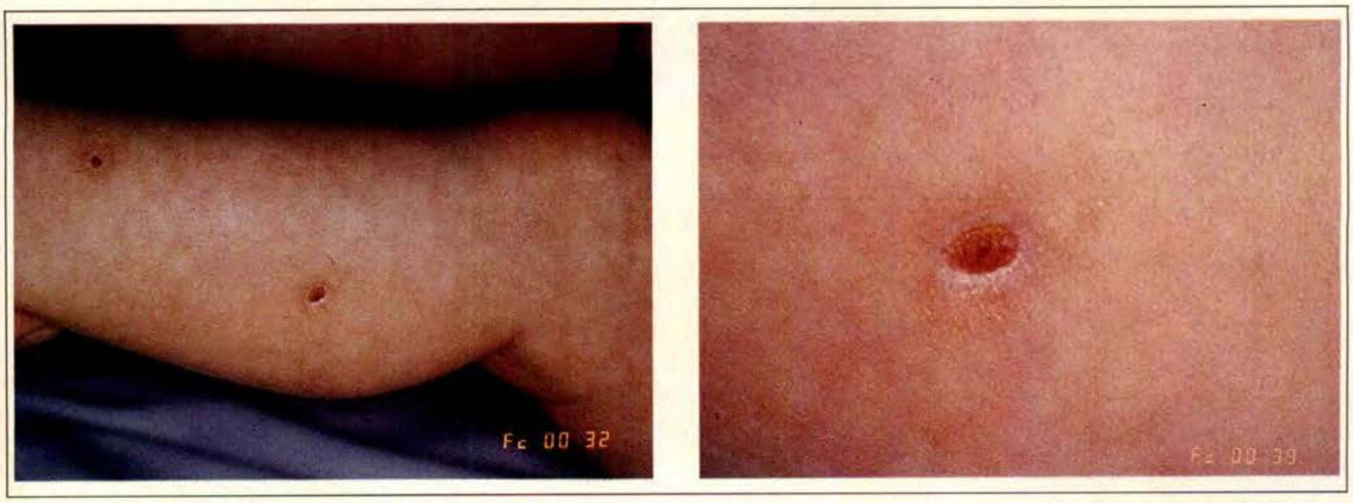

Fig 1.—*Six-week-old male infant with 10-day-old lesions on the outer aspect of the left lower leg, thought to be due to nonaccidental cigarette burns. A 35-mm single lens reflex camera with a 105-mm macro lens and a ring flash was used. Left, The lesions in relation to each other and neighboring anatomy at ×0.2 magnification. Right, The more proximal lesion at ×1 magnification, demonstrating the deeply punched out oval eschar. The eschar has a diameter of 4 mm, while the ill-defined halo of surrounding redness extends the diameter to 8 mm, the size of a cigarette. Note the databack identification code in the lower right corner.*

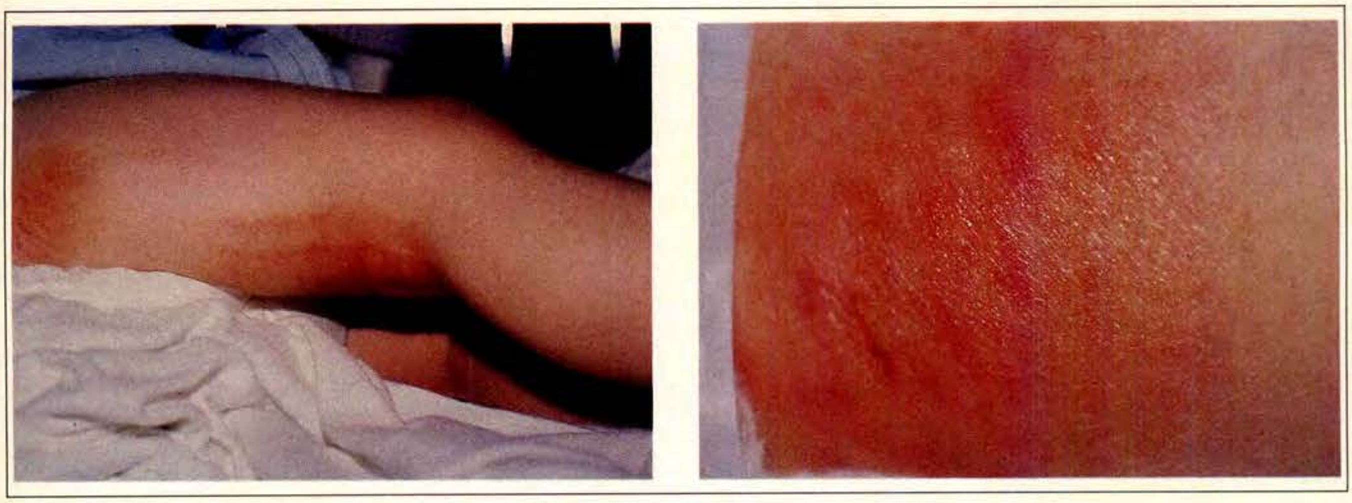

Fig 2.—*Two-year, 6-month-old male infant reported by his mother to have fallen down a set of stairs. The camera used was an auto-focus 35-mm camera with a built-in 35- to 80-mm zoom lens, macro capability up to ×0.25, and built-in flash. Left, Two abraded areas on the right posterior thigh at ×0.1 magnification. The neighboring anatomy is clearly identified, although the viewpoint is not quite parallel and the foreground is cluttered. Right, The more proximal abrasion at ×0.25 magnification, demonstrating obliquely directed linear streaking. The directional orientation of this abrasion is different from that of the distal abrasion, which appears to be oriented either horizontally or vertically. The child's mother subsequently admitted hitting the child with a rolled scatter rug.*

Some centers refrigerate or freeze film to prolong its effective shelf life. Film that is refrigerated requires 3 hours at room temperature to reach a usable temperature. If film is frozen it must be left at room temperature for 24 hours before use.[16]

Differences may be noted between film laboratories and even at the same laboratory with successive roles of film if quality control of the development process is not maintained.[15] The use of a standard commercial processing laboratory for color film is an assurance of quality control and standardization.[17]

After the film is developed, each image should be reviewed both for technique and content. No photographs, even poor ones, should be discarded. This could be misconstrued as destruction of evidence.[12,18]

A storage/filing system should be established in a cool, dry location with low light. Each slide should be stored in a clear plastic sheet to minimize handling and to allow viewing and easy storage. Kodak (Rochester, NY) slides last many years with proper use, care, and storage.[16] However, a slide used for lectures or left out in the light will fade (a washout of 1 f-stop) after only a few years.[19]

PHOTOGRAPHIC COMPOSITION

Composition is the proper arrangement of the elements in a photograph. The compositional goal of medical photography is to accurately document the patient's condition. Artistic composition is less important than consistency of technique and reproducibility of results. A technically excellent photograph or series of photographs may not be admissible as evidence if they do not establish both the scale and the anatomic location of the trauma.[1] Perspective (viewpoint), scale, and background all must be carefully considered.

Table 2.—Sample Checklist for Camera Operation

Secure lens to camera body
Remove lens cap
Secure flash to camera hotshoe
Load film
Set film speed on camera and flash
Set lens aperture (usually to automatic)
Check flash setting and turn on flash
Focus and compose the picture
Shoot
Check to be sure flash has fired
Advance film
Check to be sure film is advancing
Rewind film when done shooting
Only then open back to remove film

Medical photography must show injuries as realistically as possible and should not be used to enhance or exaggerate trauma. It is useful to photograph burns, dirty abrasions, or even unkempt children both before and after cleaning. As they change over time, lesions should be rephotographed.[1] Just as varying perspective can add a three-dimensional quality to photographic representation, so photographs of the same child over time can add a fourth dimension.

Perspective or viewpoint refers to the depiction of the relationships between objects at different distances from the camera as well as the angle from which the objects are viewed. Proper perspective as viewed in a print is very important in accurately depicting a scene. Perspective can be altered by subject-to-lens distance, lens focal length, magnification, point of view, size of the final photograph, and even the distance from which the photograph is viewed.[18] The following compositional principles should be kept in mind when photographing abused children (Table 1).

1. At least one if not several pictures should contain an anatomic landmark (Figures 1 and 2). The inclusion of an elbow or knee allows the viewer to identify the anatomic location of a wound. Anatomic or background material unnecessary to the photograph, however, should be left out. If the photographer follows this principle, the main subject will occupy a larger portion of the picture and will be easier to study. In addition, unneeded and possibly confusing visual information will be omitted.[8,15,20]

2. At least two photographs should be taken of each finding, one including identifying landmarks and one close-up with the lesion filling the frame. Magnification should be obtained in the original, not from a blowup (Figures 1 and 2).

3. The subject should be arranged in a manner that allows the surface of interest to be parallel to the film. This is done by making sure the back of the camera, the film plane, is parallel to the pathology. Likewise, the photographer and the subject should be at the same level.[8,15,20]

4. Varying perspective, taking a number of shots from different angles and distances, is quite useful, particularly since electronic flash may produce unpredictable reflections.[15,17] Additionally, since the skin is a curved surface, some lesions may require several photographs to fully reveal the pathology.

5. The picture should be composed the way an examiner would normally look at that anatomic area. The horizontal format should be primarily used. However, when necessary, such as for full-body shots, the vertical format may be used.

6. The size of lesions should, if possible, be documented on the photograph by using some measuring device, such as a metric ruler.[1,18] Photographs are no substitute, however, for clearly written and detailed descriptions of the dimension, shape, color, size, and location of lesions. Color along with size may be distorted in the photograph.

7. It is desirable but not always possible to have a standard set of views for each area of the body photographed.[14] The four cardinal anatomic positions, anteroposterior, posteroanterior, right lateral, and left lateral, should be kept in mind when photographing children. However, young children may not cooperate with such positioning plans, reinforcing the usefulness of multiple views from varying perspective.

8. Forensic bite mark photography is a specialized branch of medical photography and is best left to a forensic dentist or pathologist. The basic objective of photographing bites is the accurate recording of all aspects of the mark. Size, shape, color, depth of indentations, and three-dimensional contours must be preserved. No one medium is suitable for all these functions. Photographs, both black-and-white and color, can record the first three, whereas dental impressions show the last two. Ultimately, the photographs may be enlarged to life size and compared with representations of the suspect's teeth.[17]

9. Recording photographic data (date, time, location, case number, camera, lens, aperture, film, light source, and subject distance) helps reconstruct cases, particularly for courtroom verification, aids learning and teaching, and encourages consistent technique if more photographs are required later.

10. Background is important.[12,14,20] The background wall should be nonreflective, ideally a neutral gray, green, or blue in a matte finish. Glossy background surfaces can produce a glare. A cluttered room makes a poor background for medical photographs. Materials unnecessary for the photograph should be removed. A backdrop may be useful.

11. Before photographing children in clinical settings it is important to establish both a protocol and a checklist for operation (Table 2). Clearly identify who will take the photographs and how the film will be handled after picture taking. Always shoot a test roll first when using a new camera setup.

COMMON PHOTOGRAPHIC ERRORS

Despite the advent of simple and sophisticated electronic cameras, a number of traditional camera operation errors continue to occur.

1. The subject is blurred. This is usually caused by improper focusing, often because the photographer attempted to get closer than the minimum focusing distance of the lens to magnify the image. Sometimes, movement of the subject or camera, particularly with shutter speeds slower than 1/90 second, will also cause this, although with high-speed electronic flash this is usually not a problem.

2. The negative is clear or the transparency is black. Most likely the film was never exposed, because it did not advance in the camera. The most common cause of this is failure to properly load the film. It is important to load film correctly and ensure that the film is being transported through the camera by checking that the rewind knob turns as the film is advanced. Because of this problem, some centers recommend shooting a backup set of prints using an instant-picture Polaroid (Clifton, NJ) camera.[12]

3. The film is overexposed or underexposed. Incorrect exposure continues to be a common problem in photography despite advances in automatic exposure control. Exposure is dependent on the brightness of the image, the

camera aperture, the time the photographic material is exposed, and film speed. The usual cause of incorrect exposure is incorrect setting of the aperture, film speed, shutter speed, or flash. Camera and flash settings should be carefully checked. An exposure technique some professionals use to avoid overexposure or underexposure is bracketing. If the final combination of film and flash indicates an aperture of f-16, three frames are exposed, one at a setting of f-16, the second overexposed at f-11, and the third underexposed at f-22. One of the three will be perfectly exposed.[15,17]

4. The print or slide has distorted color, often yellow or green. This most commonly occurs because color daylight film is used indoors without a flash. Always use a flash indoors, even if the room is very bright.

PHOTOGRAPHING CHILDREN

When photographing children it is important to explain to the child what is going to happen in language the child will understand.[21] Allowing children to try out the camera and flash often aids in gaining their trust.[14] Children should be allowed to assume a position of comfort. It is far better to have a cooperative child somewhat out of optimal photographic position yet still rather than an uncooperative, moving child.

Correct anatomic relationships are not always possible with children. It is thus helpful to take many pictures in different poses. If the child will not move, the photographer should. Besides affording greater opportunity for a satisfactory photograph, multiple views add a three-dimensional quality to a two-dimensional medium.

It is often useful to involve a trusted support person in the photographic session. Apart from being a comfort to the child in unfamiliar surroundings, such a person provides an extra pair of hands.[21]

Film-advancing motor drives are extremely useful when photographing children, as are a fast-recycling flash with fresh batteries and a single zoom-macro lens.

Most critically, the photographer must remain cognizant of the potential traumatic effect of photographs on the abused child, both with regard to the photographic process itself and with regard to the use of these photographs in court.

LEGAL ISSUES

In child abuse litigation, photographs of the injured child may play an important role in helping prove nonaccidental injury. For photographs to be used as court evidence they must be properly verified and relevant.[22]

Verification requires that the photographer or physician testify that the pictures accurately portray the findings.[1] From a medicolegal perspective, photographs of abused children should convey a fair and accurate representation of the scene. The photographer should also be able to state how the photograph was taken. Pictures that are inadmissible because of technical error (out of focus, distorted, unidentifiable, too dark, etc) must be avoided.[23]

To help verify that the photographs are actually of a particular child, one picture can be taken of the child's name and one of the child's face. An identifying sign may be placed in front of the patient for each picture. The inclusion in the photograph of such signs or labels with the patient's name and date, however, is time-consuming and distracting.[8] An alternative for identification of the film is the use of a camera databack. Many 35-mm cameras have available databack attachments that imprint the time, date, and an identifying code on each frame. Another advantage of a databack is that, since the imprint is always located in the bottom right of the transparency or negative, right-left and top-bottom orientation are made simpler (Fig 1).

Once processed, the slides or prints should be labeled. Each print or slide should contain the name of the child, age, date of birth, date and time of photograph, hospital number, name of photographer, and name of physician. If confidentiality is a concern, each print or slide should, at a minimum, be labeled with a medical record number and the date the photographs were taken.[5]

Relevance is a judicial decision.[24] Photographs may have evidentiary value yet be deemed prejudicial to the defendant. Whether the probative value outweighs the prejudicial danger is a decision each trial judge must make with each case. Photographs are generally considered admissible, however, if they shed light on the issue, enable a witness to better describe the objects portrayed, permit the jury to better understand the testimony, or corroborate testimony. Courts generally permit physicians to explain and illustrate their testimony with a photograph.

The laws of a number of states refer to taking photographs in cases of suspected abuse.[1] Indeed, many states require that reasonable efforts be made by the reporting hospital staff member to take or cause to be taken color photographs of any areas of visible trauma on the child. Many states provide for immunity from civil or criminal prosecution for the reporting institution and for the person arranging for or taking photographs if done in good faith. However, a survey of professional medical photographers suggested a lack of awareness of the statutes that require photographs and provide immunity.[1]

Each institution should have a policy for both the handling and release of photographs.[1] Although an unbroken chain of evidence may be important in a criminal proceeding, in a civil case, where the photographer's testimony can verify that the photographs are representative of a particular subject, such a chain of evidence may be less critical. For an unbroken chain of evidence, film should change hands as infrequently as possible. With each transfer, the signature of an authorized recipient should be affixed to a list of the materials received, along with the date, time, and place. Outside laboratory processing may be acceptable even if the laboratory does not sign for the film, if sending film out is the normal business procedure for the institution.[18] Courts usually accept film sent to a standard commercial processing laboratory via first-class mail as an unbroken chain of custody.[25] These laboratories will, on request, enclose an affidavit ensuring the receipt, correct processing, and return of the film. The use of a standard commercial processing laboratory for color film assures quality control, standardization, and legal acceptability.

SUMMARY

The principles of medical photography are good equipment, adequate lighting, and planned composition. Equally important is a working knowledge of camera equipment, film procedure, and medicolegal implications.

Since photographs offer the only certain method of preserving often perishable findings, they may serve several useful purposes. Photographs can be reviewed after the examination to double-check findings or perhaps even to discover previously unnoticed findings. If the magnification is precisely known, measurements can be obtained directly from the photograph. Photographic findings can be discussed among colleagues and consultants. Photographs taken during an initial examination can provide a standard for subsequent comparison. Should a second opinion be required, photographs may save the child from the trauma of a repeated examination. In court, photographs can provide a powerful and convincing statement where a simple verbal description might fail. Even when not directly used in court, photographs may serve to enhance testimony by jogging the examiner's memory of specific findings.[5]

Whether child abuse has occurred and who is responsible is a legal issue for the courts to decide.[10] Corroborative physical evidence photographically documented can, however, be an important adjunct to the legal process. Physicians who perform medicolegal examinations of abused children must have access to adequate photographic equipment and a working knowledge of photographic techniques.

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Physicians, Formula Companies, and Advertising

A Historical Perspective

Frank R. Greer, MD, Rima D. Apple, PhD

• The recent advent of new advertising campaigns for infant formulas aimed at the general public via television commercials, newspapers, free formula coupons, and lay periodicals has disrupted a comfortable symbiotic relationship between infant food manufacturers and the medical profession that has endured for more than 50 years. In the late 19th century, physicians were concerned about the advertising claims of these products and generally felt that indications and directions for their use should be the province of the physician. Between 1929 and 1932, the American Medical Association, through its Committee on Foods and "Seal of Acceptance," essentially required the entire formula industry to advertise only to the medical profession. Since 1932, the US formula industry has developed into a $1.6 billion market. In 1988, Nestlé (absent from the US infant formula industry since the 1940s) acquired the Carnation Company and launched an advertising campaign to the general public for its formula products. Bristol Myers/Mead Johnson, in cooperation with Gerber Products Company, quickly followed suit. These actions threaten to once again remove the realm of infant feeding from the exclusive supervision of the medical profession. The new multimedia public advertising campaigns may increase the cost of infant formula to the general public and have a negative impact on the incidence of breast-feeding. In addition, formula advertising campaigns will likely increase the danger of advertising hyperbole and affect the level of financial support by formula companies for scientific meetings, medical research, education, and social events at medical meetings.

(*AJDC.* 1991;145:282-286)

In October 1989, millions of television viewers throughout the United States saw 30-second advertising spots extolling the advantages of Gerber Baby Formula. Earlier that year, Nestlé-Carnation launched a similar television advertising campaign to promote its formula product, Good Nature (the name was recently changed to Follow-up Formula). These commercial presentations conflicted directly with the medical profession's longstanding and effective opposition to the advertising of infant formula to the general public, and disrupted a comfortable symbiotic relationship between infant food manufacturers and the profession that had lasted for more than 50 years.

Since the early decades of this century, the formula companies have advertised to the medical profession by promoting their products extensively in professional journals and displaying them at state and national medical meetings, which they also financially supported. After 1960, they also supplied free formula to physician-dominated hospitals, including starter packs for new mothers to bring home. Additionally, during this period, infant formula manufacturers funded medical research in pediatric nutrition, particularly when the studies were related to product development.

The medical profession's negative response to the new advertising campaigns was swift. The American Academy of Pediatrics (AAP) announced a new policy refusing contributions from formula companies who marketed their products directly to the public rather than exclusively to health care providers, and the Executive Board of the AAP subsequently rejected $760 000 in pledged contributions from Mead Johnson Nutritionals and Gerber Products Company (written communication from Donald W. Schiff, MD, AAP president, to membership, September 27, 1989).[1] There were also scattered reports that Mead Johnson formula products had been stricken from hospital formularies. What were the events that led to the 50-year advertising understanding between formula companies and physicians? What factors precipitated its demise?

In the 1870s, the vast majority of American babies were fed human milk. Mothers were expected to breast-feed and the few available alternatives were considered poor and risky substitutes. During the next 75 years, however, the US infant food and formula industry developed rapidly, accompanying a dramatic shift from breast-feeding to artificial or bottle feeding. Developments in technology, science, and medicine, along with social and economic changes, fueled the transformation in infant feeding practices and established the infant formula industry. In the 1940s and 1950s, this now safe and alternative method to breast-feeding rapidly gained popularity among physicians and consumers.[2] Indeed, by 1958, 63% of all newborns were fed formula exclusively before being discharged from the hospital.[3]

Many proprietary infant foods appeared in the United States in the last decades of the 19th century. Early manufacturers usually produced a variant of the formula developed by Justus von Liebig in Germany in the 1860s.[4] In Switzerland, Henri Nestlé created his variant of Liebig's

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From the Departments of Pediatrics (Dr Greer) and History of Medicine (Dr Apple), University of Wisconsin, Madison.

Reprint requests to the Wisconsin Perinatal Center, 202 S Park St, Madison, WI 53715 (Dr Greer).

formula combining condensed milk, sugar, and wheat flour. The first Nestlé's Milk Food plant opened in 1868, and by 1873 the formula was sold in the United States and 16 other countries.[5] Companies also formed on this side of the Atlantic. James Horlick, a pharmacist, formulated another Liebig-type formula, Horlick's Malted Milk, in Racine, Wis, in 1882.[6] During the early years of the industry, manufacturers solicited the broadest audience possible, advertising both to the general public and to physicians. As is still the practice today, the inclusion of medical testimonials by the profession in the advertising copy added a veneer of "scientific" and medical respectability. In addition, the companies distributed brochures and free samples at medical conventions and advertised in medical journals.[2] During this early period, promotions in nonmedical journals advised mothers to write in for free samples and brochures.

From the beginning of the infant food industry, physicians expressed concern about direct advertising to the public. Dr Thomas Morgan Rotch, on the staff of Harvard Medical School, believed that infant foods produced and advertised by "commercial men" rather than the medical profession contributed to the high infant mortality rate.[7] Dr Rotch demanded that pediatrics "rescue" infant feeding from "the pretensions of proprietary foods."[7] Thus, despite the 19th-century manufacturers' attention to physicians, the medical profession resisted and debated the use of infant formula products and opposed their direct advertisement to laypersons. Undoubtedly, these physicians believed that the indications and guidelines for the use of these products were the province of the medical profession.

An 1888 American Medical Association (AMA) Subcommittee on Infant Feeding clearly documented a lack of uniformity among physicians regarding infant feeding,[8] but most physicians unquestionably preferred breast-feeding, with bottle feeding being strongly associated with the high infant mortality rates. In fact, the ward for artificially fed infants of the New York (NY) Foundling Asylum was known as the "ward of the dying babies."[4] During this period, a growing proportion of general medical practice concerned the safe feeding of infants and the specialty of pediatrics emerged as a group of physicians particularly interested in promoting good infant nutrition and hygiene.

Between 1890 and 1910, these early pediatric researchers advocated the cleanup of infant milk supplies, including improving the quality and care of dairy herds, the establishment of infant milk depots and clinics for the distribution of "clean milk" to the public, and the founding of milk laboratories.[2] The latter change was a direct result of the dominant theory of infant feeding of the period, Rotch's percentage method.[9] He insisted that infants were to be fed a certain percentage of each known food element (ie, fat, protein, and carbohydrate) in proportions dictated by the individual's needs. Rotch believed that minute variations (as little as 0.1%) in the composition of the food could make a difference in its digestibility and healthfulness. As many as 19 formulations were recommended for healthy infants during the first year of life. Minute changes were made on weekly and even daily bases and elaborate tables and mathematical formulas were published to optimize Rotch's principles. Therefore, the need for laboratories to compound the required formulations developed. By 1910, growing numbers of studies in infant nutrition demonstrated the inadequacy of the percentage method. The most important data of this research supported the caloric method of infant feeding, the method that persists to this day.[10]

Despite continued medical criticism of commercial foods, a significant and increasing number of physicians did advise their patients to use these products. Physicians, rather than ignoring all commercial foods, became mediators between manufacturers and consumers. Henry Tuley, MD, writing in *JAMA* in 1899, concluded, "The method of artificial feeding which will prove most popular with the laity must embody two requisites: cheapness and ease of preparation. On the physician devolves the great burden of educating people beyond the indiscriminate use of proprietary foods, and the importance of accuracy in the preparation of the food prescribed."[11] Thus, given the complexities inherent in these early infant "percentage" formulas, both for the physician to calculate and for the mother to prepare, it was easier for busy practitioners to give up the whole program in despair and "resort to the use of the patent baby foods as the easiest way out of the difficulty," opined Eugene Darling, MD, in 1911.[12] Unfortunately, once this occurred, the mother could follow the printed instructions on the product and did not need to return to the physician for further supervision. Such a situation could be physically unhealthy for the infant and potentially economically harmful to the physician.

In 1910, J. S. Leopold, MD, returning to New York City from Germany, reported that the German use of dextrin and maltose in infant formulas resulted in improved tolerance and digestibility. Unable to find a source of this sugar in the United States, he convinced the Mead Johnson Company to manufacture and distribute Dextri-Maltose.[13] Dextri-Maltose was evaluated at the Babies Ward of New York (NY) Postgraduate Hospital, and was the first example of an infant food product developed through the cooperation of an investigative pediatric researcher and a private company. With its initial promotional efforts, Mead Johnson began a trend in the industry by deciding that gaining the respect and goodwill of the medical community could be potentially more profitable than marketing the product directly to the public.

Accordingly, the company unveiled Dextri-Maltose at the 1912 AMA convention and promoted this milk modifier, as well as its later infant feeding products, exclusively to the medical profession. No directions appeared on the package. Wheel "feeding calculators" and formula prescription blanks imprinted with the physician's name and address were supplied to physicians. Such prescriptions told the mother how to mix the formula and feed it to her child, and reminded her to bring the baby back to the physician for a checkup and new formula on a specified date. Mead Johnson announced its policy in many of its advertisements and brochures for physicians, frequently stressing that "when Dextri-Maltose is used as the added carbohydrate of the baby's food, the physician himself controls the feeding problems."[14]

Following Mead Johnson's success, other companies emulated the company's so-called "ethical" policy of infant food advertising. In 1915, H. J. Gerstenberger, MD, of Western Reserve University, Cleveland, Ohio, formulated an infant milk food that was closer to human milk than any other popular artificial feeding product of its day. In this product, human milk fat was approximated for the first time by a blend of homogenized vegetable and animal fats. Gerstenberger presented this infant food at the 1915 meeting of the American Pediatric Society after testing it at the Babies Dispensary and Hospital in Cleveland.[15] The Laboratory Products Company (eventually bought by

Wyeth Laboratories) subsequently produced and distributed Gerstenberger's formulas under the name S.M.A. (Synthetic Milk Adapted) and directed its advertising campaign primarily toward physicians. Although a few advertisements did appear in the early years in lay journals such as *Hygeia*, actually published by the AMA, the advertising copy typically stated that S.M.A. was "to be used only under the direction of the physician."

The commercial success of Dextri-Maltose and S.M.A., both produced by companies new to the infant feeding industry, demonstrated to other companies that such advertising policies could result in a satisfactory compromise between the needs of the manufacturers to sell their products and the desires of physicians to control the distribution and use of infant foods. Although the Nestlé Company, unlike Mead Johnson and Laboratory Products, continued to advertise its milk food in lay journals and to offer mothers free samples and booklets, the company announced a new product, Lactogen, in 1924 "sold only on the prescription or recommendation of a physician. No feeding instructions appear on the trade package." At about the same time, the Horlick Company developed its Horlick's Milk Modifier, which was "offered for sale on physician prescription only."[2]

Another aspect of the infant food industry, the manufacture and promotion of evaporated milk formulas, showed a similar pattern. In 1929, W. M. Marriott, MD, of Washington University, St Louis, Mo, published a controlled study comparing evaporated milk formula, human milk, and bottled cow's milk formula.[16] The infants fed evaporated cow's milk formula showed better weight gain during the first week of life than the other infants; moreover, over the long term, those infants fed evaporated cow's milk formula grew as well as those fed human milk or bottled cow's milk formula. The evaporated milk industry quickly cited Marriott's studies in advertising and informational brochures for physicians. The Pet Milk Company even hired Marriott as a consultant to show the company's sales personnel the right and wrong ways to contact physicians.[17] By 1935, evaporated milk formulas dominated infant feeding and as late as 1956, 80% of all formulas used in hospital nurseries in the United States were some dilution of evaporated milk.[18]

Clearly, the apparent success of companies such as Mead Johnson and Laboratory Products resulted in the willingness of the infant food manufacturers to forego public advertising and to direct their attention to the medical profession. Additionally, direct pressures from the medical profession spurred the demise of promotions to the laity. In 1923, the Philadelphia Pediatric Society urged the AMA to halt infant food advertising in its lay journal *Hygeia*. Such advertising, the society contended, implied recommendations by the members of the American Medical Association "[which] will tend to undo all the work which thousands of members of the medical profession have been trying to accomplish in the education of the public to the fact that infants cannot be fed in this indiscriminate manner."[19]

Although advertisements continued to appear, in 1924 the Section on Diseases of Children of the AMA established a committee "to investigate the general question of advertising of proprietary foods in medical journals and to the laity."[20] In its 1925 report, the committee acknowledged the significance of infant food products in medical practice and concluded that "it is impractical at the present time to dispense entirely with all proprietary foods." While stressing the nutritional importance of breastfeeding and "the dangers of artificial feeding of infants, particularly when carried out without supervision of medical men," it found heartening the "disposition on the part of many manufacturers of proprietary foods to cooperate with the medical profession and its medical journals."[21]

Four years later, the AMA established its Committee on Foods, within the Council on Pharmacy and Chemistry, to approve the composition and advertising claims of food products in general. Infant food companies, including evaporated milk producers, quickly presented their products for AMA approval and its "Seal of Acceptance." In 1932, the committee published specific advertising guidelines for infant foods. These insisted that "every infant, breast-fed, and doubly so, the artificially fed should be under the supervision of the physician who is experienced and skilled in the care and feeding of infants."[22] The new rules sought to restrain manufacturers from distributing directions for formulas to nonmedical personnel, reasoning that "The feeding of an infant by routine feeding formulas and instructions distributed by food manufacturers, or according to directions, printed material, or advice of any person other than the attending physician who can personally observe the condition of the baby, may seriously endanger the health of the infant. The promulgation of feeding formulas in advertising to the laity is considered to be in conflict with the best experience, authoritative judgment, and basic principles in infant feeding, and is not permissible."[22]

Nestlé did not have to change its Lactogen promotions, but the company did stop advertising Nestlé's Milk Food to the general public and limited distribution of feeding directions to physicians only.[2] Most, but not all, other companies and evaporated milk producers followed suit. The labels and advertising for Horlick's Malted Milk continued to "present explicit infant feedings formulas for infants age one week to 12 months." Despite the committee's recommendation that the company alter its advertising copy, Horlick's refused. The committee stated, "The manufacturer when informed of these opinions expressed himself unwilling to remove the feeding formulas from advertising addressed to the public for merchandising reasons. The acceptance of Horlick's Malted Milk is being withdrawn for the preceding reasons; the product will therefore no longer be listed among the committee's accepted foods."[23]

The withdrawal of the AMA's previous acceptance of Horlick's Malted Milk meant that the company could no longer advertise in AMA publications or participate in AMA meetings. Furthermore, many medical journals, such as the *New England Journal of Medicine*, received advertising contracts through AMA's Cooperative Medical Advertising Bureau.[24] This group would approve copy only for "drugs, therapeutic agents and food which are acceptable to the respective approving committees of the American Medical Association." As a result, withdrawal of the Committee on Foods' acceptance further limited Horlick's promotional activities by preventing the company from advertising in other major medical journals.

The subsequent demise of Horlick's in the United States is more complex than this analysis suggests, but it is true that the action of the committee significantly lessened the use of Horlick's products in infant feeding. Companies that allowed the AMA committee to approve their promotional material fared much better. As Mead Johnson cogently explained, "When mothers in America feed their babies by lay advice, the control of your pediatric cases passes out of your hands, doctor. Our interest in this important phase of medical economics springs, not from any motive of altruism, philanthropy or paternalism, but rather from a spirit of enlightened self-interest and cooperation because [our] infant diet materials are advertised only to you, never to the public."[25]

By the 1930s, simplified, standardized, and inexpensive artificial infant food products were widely available in this country. They contained appropriate amounts of nutrients, were free of pathogenic bacteria, and were generally accepted by the medical profession as a safe alternative to breast-feeding. Also, by this time, physicians and infant food companies had established a beneficial, reciprocal relationship.[26] In 1933, a Pennsylvania practitioner counted no fewer than 17 advertisements for infant foods in a single issue of *JAMA*.[27] Elaborate presentations by infant food manufacturers appeared at medical conventions. Ties between the formula companies and academic medicine were also well established through the funding of scientific meetings and the open support of published infant nutritional research. What happened to change this advantageous 50-year association between physicians and the formula companies?

In the late 1960s and 1970s, world attention was focused on the declining incidence of breast-feeding and the associated increasing infant mortality in some third world countries. This decline was in part attributed by physicians and laypersons to the marketing and advertising of infant formulas by international companies to the mothers in these countries. Families were often unable to maintain adequate supplies of formula without making severe economic sacrifices and lacked the necessary sanitary facilities for formula preparation and storage. Furthermore, many mothers were unable to read and/or follow the directions for safe formula preparation. In truth, no scientific data were ever presented that could separate the effects of marketing infant formulas from other causes for the decline in breast-feeding in these countries. These factors included the negative overall influence of western culture with its acceptance of formula feeding, the increasing urbanization of the population, the economic necessity for mothers to work outside the home in urban areas, and the negative effects of government health services in those countries distributing free milk powder and Western ways of infant medical care in general.[28]

Ultimately, Nestlé was singled out and an international boycott of its products was organized by INFACT (Infant Formula Action Coalition), a group that drew on existing organizations committed to curbing infant formula promotions in third world countries.[29] The controversy led to US Senate hearings in 1978, chaired by Sen Edward Kennedy (D, Mass), on the subject.[29] The World Health Organization became involved and adopted its *International Code of Marketing of Breast-Milk Substitutes* in 1981.[30] Article 5.1 of the code stated that "There should be no advertising or other form of promotion to the general public of products within the scope of this Code." Subsequently, the formula companies largely complied with these guidelines for marketing their products in third world countries. Ironically, all countries endorsed this code except the United States, citing concerns about possible restraint of trade infringements and violations of the US Constitution.

Closer to home, by the 1970s and 1980s, notwithstanding the nationwide surge in the incidence of breast-feeding, the vast majority of infants aged 3 months and older were receiving commercial formula preparations as the US infant formula industry evolved into a $1.6 billion market. In 1988, Abbott Laboratories (parent company of Ross Laboratories) and Bristol Myers (parent company of Mead Johnson Nutritionals) had a virtual lock on this lucrative market. Nestlé, absent from the United States since the 1940s, was poised to reestablish its presence. As a first step, the company acquired the Carnation Company and its image of the "Carnation baby," familiar to millions of Americans who had been fed Carnation evaporated milk formula in the 1940s and 1950s (*Wall Street Journal*. February 16, 1989:A-1).

In June 1988, Nestlé-Carnation introduced two infant formulas to the United States market. The first, Good Start H.A., was a "hypoallergenic" product for the sensitive, colicky newborn. Its advertising, which the company called an "informational campaign," was directed to the general public and made no specific mention of the formula, yet its scientific benefits were pushed vigorously to the medical profession. The second formula, Good Nature (now Follow-up Formula), was designed for older infants weaned from the breast and would, in theory, not discourage breast-feeding. It became the first infant formula marketed directly to the public on US television. Additionally, for the first time in half of a century, an infant formula, Good Nature (Follow-up Formula), was widely advertised in lay journals and newspapers. Within a short time, Nestlé-Carnation captured between 2% and 4% of the US formula market, although its proportion has since fallen somewhat (*Wall Street Journal*. June 15, 1989:B-3).[1]

Subsequently, Good Start H.A. has fallen on hard times. Public advertising has been discontinued since the product was found to be not so "hypoallergenic," and reports of severe allergic reactions to the formula appeared in the press. However, although the company has discontinued television advertising and despite extensive pressure from the medical profession and most prominently the AAP, Follow-up Formula continues to be advertised in lay journals.

With the sudden success of Nestlé-Carnation in the United States, Bristol Myers entered into an agreement with Gerber Food Company to produce Gerber Baby Formula and to market it directly to the public (*Wall Street Journal*. June 15, 1989:B-3). Not only was the product promoted on US television, but free formula coupons and free formula samples were mailed to 1.6 million new mothers throughout the United States.[31] The company argued that this was no different from supplying mothers with take-home samples of their competitors' products at the time of discharge from the hospital. Interestingly, the Gerber Baby Formula is a former Mead Johnson product that was discontinued in the early 1980s in favor of a new "superior" and heavily advertised product.

This new marketing strategy has resulted in strong reactions from the American medical community. Although the AMA has a smaller role in setting infant nutrition policies than it did 50 years ago, it recently confirmed its opposition to the direct advertising of infant formula in the United States.[32] An official statement was made by the AAP before the US Senate Judiciary Subcommittee on Antitrust, Monopolies and Business Rights at its May 29, 1990, hearing on "Advertising of Infant Formula." In this statement, the academy officially opposed any form of direct advertising to the public for the following reasons: (1) negative effect on breast-feeding; (2) interference with the patient-physician relationship regarding nutritional advice; (3) advertising hyperbole leading to consumer confusion; and (4) the impact of large-scale public advertising on the cost of infant formula.[33] The AAP did not comment, however, on the negative impact that large-scale advertising might have on the financial support that the formula industry has made available to physicians for scientific meetings, medical research, education, and social events.

It does not take a crystal ball to predict that if Gerber, Bristol Myers, and Nestlé-Carnation are successful with their new marketing strategies, then other infant formula manufacturers may follow with direct public advertising. This will once again remove the realm of infant feeding from the supervision of the physician and will likely have a negative impact on the incidence and duration of breastfeeding. Of importance economically is the potential effect of new multimedia, public advertising campaigns on the cost of infant formula. Although the new marketing strategy will not have the economic impact on medical practice it would have had 50 or more years ago, it will permanently alter the mutually beneficial relationship between the medical profession and the infant formula industry.

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Article

Ventriculitis in Newborns With Myelomeningocele

Edward B. Charney, MD; Jeanne B. Melchionni, RN; Donna L. Antonucci, MD

• **It has frequently been cited that a delay in back closure of beyond age 48 hours in newborns with myelomeningocele is associated with an increased risk of ventriculitis. It has been suggested that antibiotic therapy prior to surgery might minimize this risk. We reviewed our experience with ventriculitis in newborns with myelomeningocele and its relationship to antibiotic usage and time of back closure. Of 186 newborns, ventriculitis developed in 13 (7%), and there was no observed difference by time of back closure, clinical severity of infant at birth, status of myelomeningocele sac at birth, or type of delivery. There was a significant association between antibiotic usage and ventriculitis among the infants with delayed surgery, of which only one (1%) of 73 receiving broad-spectrum antibiotic prophylactic therapy developed ventriculitis compared with five (19%) of the 27 who did not receive antibiotics. Our data support the suggestion that antibiotic treatment is effective in minimizing the risk of ventriculitis among infants with myelomeningocele undergoing surgery after 48 hours of age.**

(*AJDC.* 1991;145:287-290)

It is often stated that surgical closure of the back lesion in a newborn with myelomeningocele is an emergency, and a delay of more than 48 hours is associated with significant increase in mortality and morbidity.[1-5] An often-cited risk of delayed surgery has been the increase in ventriculitis, with reports of an 8% incidence of central nervous system infection with immediate surgery compared with a 25% to 40% incidence among infants with surgery delayed for more than 48 hours.[6] In a previous study,[7] we concluded that surgical intervention for newborns with myelomeningocele was not an emergency because, irrespective of whether surgery was done on day 1 or day 7 of life, there was no difference in mortality or morbidity. Our data suggested that the use of prophylactic antibiotics might be effective in minimizing the previously reported increased risk of central nervous system infection or ventriculitis during that period. We wanted to assess further what factors might influence the development of neonatal ventriculitis among infants with myelomeningocele receiving surgical intervention, and whether antibiotic use prior to surgical closure of the back lesion is protective.

PATIENTS AND METHODS

We reviewed the hospital records of 186 consecutive newborns with myelomeningocele surgically treated at the Children's Hospital of Philadelphia (Pa) between 1978 and 1987. Data collected included the following: level of motor paralysis; type of delivery (vaginal or cesarean section); associated adverse criteria[8] (gross paralysis of the legs with, at most, active hip flexors; clinically evident kyphosis or scoliosis; congenital hydrocephalus with head circumference greater than the 95% percentile; birth injury; or other severe birth defects) to reflect clinical severity at birth; status of sac (leaking or intact) overlying the neural tube defect; time of back closure ("early" defined as within 48 hours, "delayed" defined as between 3 and 7 days, and "late" defined as after 1 week); time of ventricular shunt procedure; use of broad-spectrum antibiotics prior to back closure (type or combination and duration of treatment); and the occurrence of ventriculitis as defined by culture-positive ventricular fluid within the first month of life. The data were analyzed by χ^2 two-way contingency tables with Yates' correction for continuity, with statistical significance being defined as $P<.05$.

RESULTS

Patient Population

All infants were transferred to the Children's Hospital of Philadelphia for their initial treatment within the first 24 hours of life with local back care consisting of sterile saline–soaked gauze applications. Of the 186 infants with myelomeningocele receiving neurosurgical intervention, 74 (40%) had high lumbar or thoracic paralysis, 47 (25%) had midlumbar paralysis, and 65 (35%) had low lumbar or sacral paralysis. Sixty-seven (36%) were delivered by cesarean section, and 119 (64%) were vaginal deliveries. One hundred twelve (60%) had no adverse criteria at birth, whereas 51 (27%) had one, and 23 (12%) had two or more. The sac was intact in 82 (44%) and leaking in 104 (56%). No sac that was initially intact leaked prior to surgical closure. One hundred sixty-two (87%) received ventricular shunts for hydrocephalus within the first 8 weeks of life.

Of the 186 infants, 86 (46%) had early surgical closure of the back lesion, 78 (42%) had delayed closure, and 22 (12%) had late closure, based on time of parental consent for surgical management. Of the 82 infants with intact sacs, 41% had early, 48% had delayed, and 11% had late surgery compared with the 104 infants with leaking sacs, of whom 50% had early, 38% had delayed, and 12% had late surgery. Of the 119 infants delivered vaginally, 50% had early, 42% had delayed, and 8% had late surgery compared with the 67 infants delivered by cesarean section, of whom 39% had early, 43% had delayed, and 18% had late surgery. These differences were not significant. There was, however, a significant difference ($P<.05$) between those infants with no adverse criteria and those with one or more with regard to time of surgery. Of the 112 infants

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From the Department of Pediatrics, University of Pennsylvania School of Medicine, Philadelphia, and the Division of Child Development and Rehabilitation, Children's Seashore House at the Children's Hospital of Philadelphia.

Reprint requests to the Children's Hospital of Philadelphia, 34th St and Civic Center Blvd, Philadelphia, PA 19104 (Dr Charney).

Infants With Ventriculitis*

Infant No.	Type of Delivery	No. of Adverse Criteria	Status of Sac	Time of Back Closure, d	Time of Ventricular Shunt, d	Age at Positive CSF Culture, d	Antibiotics (Duration in Days)	Organism
1	Vaginal	2	Intact	4	6,14	17	Ampicillin sodium, gentamicin sulfate (7)	*Escherichia coli*
2	C-Section	0	Intact	2	42	9	Ampicillin sodium, gentamicin sulfate (4)	*E coli*
3	Vaginal	1	Intact	2	2	2	Oxacillin sodium, gentamicin sulfate (4)	*E coli*
4	C-Section	0	Leaking	1	4	16	Ampicillin sodium, gentamicin sulfate (6)	enterococcus
5	Vaginal	0	Intact	1	14	28	Ampicillin sodium, gentamicin sulfate (3)	*Staphylococcus aureus*
6	C-Section	0	Leaking	1	3	8	Ampicillin sodium, gentamicin sulfate oxacillin sodium (5)	*Staphylococcus epidermidis*
7	Vaginal	0	Leaking	4	8	13	. . .	*E Coli*
8	Vaginal	0	Intact	3	. . .	4	. . .	*E Coli*
9	Vaginal	0	Intact	2	24	11	. . .	*E Coli*
10	Vaginal	0	Intact	2	29	6	. . .	*E Coli*
11	C-Section	3	Leaking	19	14	25	. . .	Group B *Streptococcus*
12	Vaginal	0	Intact	19	14	25	. . .	Group B *Streptococcus*
13	C-Section	0	Intact	4	18	24	. . .	*Klebsiella pneumoniae*

*CSF indicates cerebrospinal fluid, and C-Section, cesarean section.

with no adverse criteria, 61 (54%) had early surgery compared with 24 (32%) of the 74 infants with one or more adverse criteria.

Antibiotic Use

A total of 131 newborns (70%) received antibiotic prophylaxis within the first 24 hours of life and prior to surgical closure of their back lesion, at the discretion of the neurosurgeon, without apparent influence of type of delivery, status of sac, or clinical severity of the condition. Antibiotics were received by 79 (66%) of 119 infants delivered vaginally and 52 (78%) of 67 infants delivered by cesarean section; by 55 (67%) of 82 infants with intact sacs and 76 (73%) of 109 infants with leaking sacs; and by 77 (69%) of 112 infants with no adverse clinical criteria and 54 (73%) of 74 infants with one or more adverse criteria at birth.

Fifty-nine (69%) of the early surgery group, 61 (78%) of the delayed group, and 11 (50%) of the late surgical group received therapy. Mean durations of therapy for the early, delayed, and late groups were 4.6 days (range, 1 to 14 days), 6.1 days (range, 1 to 14 days), and 8.5 days (range, 1 to 18 days), respectively. These differences were not significant. Antibiotic usage included a combination of ampicillin sodium (100 mg/kg per 24 hours in two divided doses) and gentamicin sulfate (5 mg/kg per 24 hours in two divided doses) in 92 infants (70%); oxacillin sodium (100 mg/kg per 24 hours in two divided doses) and gentamicin sulfate in 21 infants (16%); and vancomycin hydrochloride (20 mg/kg per 24 hours in two divided doses) and gentamicin in six infants (5%). Other antibiotic regimens included use of nafcillin sodium, kanamycin sulfate, tobramycin hydrochloride (20 mg/kg per 24 hours in two divided doses) and gentamicin in six infants (5%). Other antibiotic regimens included use of nafcillin, kanamycin, and tobramycin sulfate.

Ventriculitis

Thirteen (7%) of 186 infants developed ventriculitis within the first month of life (Table). All but one (infant 3) underwent a clinical deterioration (eg, lethargy and fever) that necessitated cerebrospinal fluid culture for diagnostic evaluation. The age at which culture-positive ventricular fluid was obtained varied from 2 to 28 days, with a mean of 14 days. Isolated organisms among the 13 infants included: *Escherichia coli* in seven, group B *Streptococcus* in two, *Staphylococcus epidermidis* in one, *Staphylococcus aureus* in one, *Klebsiella pneumoniae* in one, and enterococcus in one. In vitro resistance to ampicillin sodium was noted in three of the seven *E coli* isolates and to gentamicin sulfate in the *S epidermidis* isolate. Positive ventricular fluid cultures were obtained prior to the insertion of a ventricular shunt in six infants, whereas seven had organisms isolated within 4 to 14 days after a ventricular shunting procedure. Of these seven, all but one (infant 6) had organisms that were typical for sac colonization, rather than for acquisition during a shunting procedure. Positive cultures were obtained between 3 and 10 days after antibiotics were discontinued in infants 1 (10 days), 2 (5 days), 4 (10 days), and 6 (3 days). Infant 3 had a positive cerebrospinal fluid culture on 2 of the 4 days of antibiotic coverage, whereas infant 5 had a positive culture 25 days after a 3-day course of antibiotics was discontinued.

As shown in the tabulation below, there was no observed significant difference in the occurrence of ventriculitis by type of delivery, clinical severity of infant (associated adverse criteria), status of myelomeningocele sac at birth, or time of back closure.

Variables (No.)	No. (%) of Infants With Ventriculitis
Type of Delivery	
Cesarean section (67)	5 (7)
Vaginal (119)	8 (7)
Adverse Criteria	
None (112)	9 (8)
One (51)	2 (4)
More than two (23)	2 (9)
Status of sac	
Intact	9 (11)
Leaking (104)	4 (4)
Time of back closure	
Early (86)	7 (8)
Delayed (78)	5 (6)
Late (22)	1 (15)
Antibiotic prophylaxis	
Early surgery	
Yes (59)	5 (8)
No (27)	2 (7)
Delayed or late surgery (*P*=.005)	
Yes (73)	1 (1)
No (27)	5 (19)

Antibiotic use did not significantly affect the development of ventriculitis among the infants with early surgery; however, of the 100 infants with delayed or late surgery, only one (1%) of 73 receiving broad-spectrum antibiotic prophylactic therapy developed ventriculitis compared with five (19%) of the 27 who did not receive such therapy. This difference is highly significant at $P=.005$ by χ^2 testing with Yates' correction for continuity. Of the five infants with early surgery and ventriculitis, mean duration of therapy was 4.4 days compared with a mean of 4.6 days among the 54 infants with early surgery and no ventriculitis. Infant 11, with delayed surgery and ventriculitis, initially received antibiotics for 7 days, compared with a mean of 6.1 days for the 60 infants with delayed surgery and no ventriculitis.

COMMENT

Central nervous system infection in any neonate is associated with high morbidity and mortality, even in those infants receiving early and appropriate treatment at the time of diagnosis. Most of the investigative work in evaluating various strategies to prevent this condition has focused on early-onset group B streptococcal disease with trials of chemoprophylaxis in selected mothers and/or infants.[9,10] All infants with myelomeningocele are at an increased risk of central nervous system infection, as the abnormally covered neural elements of their backs are exposed to the normal intrapartum bacteria and postpartum nosocomial skin colonization. The factors that influence the conversion from bacterial colonization to disease in the normal newborn are not well understood, and little investigation has been done in evaluating strategies for preventing infection in the myelomeningocele newborn population.

The development of ventriculitis in our population of newborns with myelomeningocele was found not to be associated with the timing of surgical intervention for the back lesion, status of the back lesion, clinical severity of the condition, or the type of delivery. There were, however, data to support our earlier suggestion[7] that broad-spectrum antibiotic prophylaxis is effective in minimizing the risk of ventriculitis among infants receiving surgical intervention after 48 hours of age. This observation is contrary to the often-cited argument advocating a need for early surgery to avoid ventriculitis. Since there was no apparent influence of type of delivery, status of sac, or clinical severity of the condition on whether antibiotic prophylaxis was received, it appears that clinical bias for antibiotic usage, which might have influenced our final results, did not exist.

The development of ventriculitis in the six infants with chemoprophylaxis requires further comment and speculation. Infants 2 and 5 had bacterial organisms (*E coli* and *S aureus*, respectively) that were resistant to ampicillin sodium but sensitive to gentamicin sulfate, which has relatively poor cerebrospinal fluid penetration.[11] Infant 6 had *S epidermidis,* which was resistant to all three antibiotics used for chemoprophylaxis. Infant 3 had an *E coli* organism sensitive to both ampicillin sodium and gentamicin sulfate isolated at 2 days of age, and may have had in utero-acquired disease rather than postpartum colonization-conversion to disease.

On the basis of our data, we conclude and recommend that chemoprophylaxis should be used routinely in newborns with myelomeningocele, especially in those for whom there may be a delay in surgical management. This is particularly relevant for hospital delivery settings in which the newborn may require transport to a hospital with a multidisciplinary team specialized in the care of children with myelomeningocele and their families. In our review of the factors that might have influenced the timing of surgical intervention, we observed that a delay in surgery was more common among infants with one or more adverse criteria. Since the time of surgery was based on time of parental consent, we may assume that for many of the parents with more severely involved infants, additional time was necessary to make a decision regarding surgical management. It is for these families that a "decision making process is best handled in an atmosphere wherein feelings of emergency or urgency are minimized and time for parental discussion is maximized."[7]

The finding that some infants developed ventriculitis in spite of chemoprophylaxis allows us to suggest some modification in therapeutic strategy. First, trials of a more effective chemoprophylactic regimen may be indicated, since three of our six "failures" had organisms that were not effectively treated by the ampicillin sodium and gentamicin sulfate regimen. The use of a third-generation cephalosporin, such as cefotaxime sodium, with its broad spectrum of activity against both gram-positive and gram-negative organisms, high-level resistance to hydrolysis by β-lactamase, enhanced blood-brain barrier penetration, and cerebrospinal fluid bactericidal activity,[12] in combination with vancomycin hydrochloride for *S epidermidis* coverage may provide more effective chemoprophylaxis. In addition to use during the first week of life, similar chemoprophylaxis might be reinstituted just before and several days after any neurosurgical procedure during the first month. The aforementioned interventions are speculative and require additional investigative work before specific guidelines may be established. We hope that implementation of such guidelines might further minimize the risk for ventriculitis in all newborns with myelomeningocele.

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Article

Stimulant Medication and Attention Deficit–Hyperactivity Disorder

The Child's Perspective

Jennifer Bowen, MBBS; Terence Fenton, PhD; Leonard Rappaport, MD

• Fifty-eight children receiving stimulant medication for attention deficit–hyperactivity disorder at referral clinics for learning disabilities at two teaching hospitals in Massachusetts were invited to participate in a study of their knowledge and attitudes. The 45 respondents and parents completed separate questionnaires concerning how they felt about receiving stimulant medication. Eighty-nine percent of the children felt that the medication was helpful and 78% liked or were indifferent to it despite a high rate (85%) of reported side effects. The five children (11%) who responded that they would stop taking stimulant medication if they could were more likely to perceive the medication as unhelpful and were receiving standard methylphenidate hydrochloride rather than a long-acting preparation. We conclude that children's perspectives on medication should be elicited directly and sustained-release medication may be more acceptable to children with attention deficit–hyperactivity disorder.

(*AJDC.* 1991;145:291-295)

Stimulant medication has been used in the treatment of children with attention deficit–hyperactivity disorder (ADHD) for over 50 years,[1] yet its use still causes intermittent controversy and adverse publicity in the media.[2] There is, however, a general consensus among physicians that stimulant medication is useful in the treatment of ADHD,[3] particularly as part of a multimodal approach to treatment.[4,5]

Ideally, children who are treated with stimulant medication are allowed to be active participants in their own treatment, yet response to treatment is usually determined by asking parents and teachers about changes in the child's behavior. To our knowledge, only a few studies[6-9] have assessed children's perceptions of the effects of stimulant medication and how children feel about receiving such treatment. These studies have shown that children are generally knowledgeable about the purpose of their medication, but have mixed feelings about taking it. Many children have been found to dislike taking stimulant medication even if they feel that it is helping them. Few studies, however, have examined in detail the differences between children who dislike medication and those who like, or are indifferent to, taking medication.

Recent studies[10-12] have shown that compliance in the use of stimulant medication is poor, and it has been suggested that this may be a factor in the relatively poor long-term outcomes in some studies of children treated with stimulant medication. Because a child's dissatisfaction with stimulant medication may have significant implications for compliance, it seems important to increase our knowledge of factors associated with children's attitudes toward stimulant medication. The purposes of the current study were to: (1) assess the general feelings, knowledge, and attitudes of children with ADHD who are being treated with stimulant medication as part of a multimodal approach to treatment; (2) assess the impact of recent adverse media publicity on these children; (3) compare the children's perceptions concerning the effects of the medication with those of their parents; and (4) examine factors that may distinguish children who generally dislike taking stimulant medication from other children.

PATIENTS AND METHODS

Questionnaires were sent by mail to 58 children with ADHD and their parents. The children were all between ages 8 and 18 years, were receiving stimulant medication, and had been doing so for at least 6 months. The children were all patients in programs for children with problems at school at Children's Hospital, Boston, Mass, or the Franciscan Children's Hospital, Boston. The children had been diagnosed as having ADHD by a multidisciplinary team consisting of a pediatrician, a psychoeducational specialist, and a child psychologist or psychiatrist. Diagnoses were made on the basis of parent interview, parent and teacher ANSER questionnaires, and neurodevelopmental, psychoeducational, psychological, and medical assessments. This protocol was approved by the committee on human investigation.

All children in the study met with the *Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition*[13] criteria for moderate or severe ADHD. All were in at least the average range of intelligence and none had gross neurologic damage or psychosis. As reported by parents and teachers, all the children had shown a positive response to stimulant medication (methylphenidate hydrochloride or dextroamphetamine sulfate). In addition to the stimulant medication, children were receiving a variety of other services as part of a multimodal approach to treatment based on findings at the time of the initial assessment. Children were reviewed every 3 to 6 months by their physician and other members of the assessment team.

The children's questionnaires were designed to assess their

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From the Division of Ambulatory Pediatrics, Children's Hospital, Boston, Mass.

Reprint requests to Children's Hospital, Fegan 6, 300 Longwood Ave, Boston, MA 02115 (Dr Rappaport).

Table 1.—Comparison of Children who Returned Questionnaires With Those Who Did Not

Characteristics	Respondents (n=45)	Nonrespondents (n=13)	*P*
1. Age, y (mean ± SD)	11.9 ± 2.4	12.5 ± 2.7	.82*
2. Duration of medication, y	3.3 ± 2.0	3.7 ± 1.5	.47*
3. Males	41 (91.1%)	12 (93.3%)	.89†
4. Sustained-release medication‡	28 (62.3%)	8 (61.5%)	.92†

**t* test for differences between independent variables.
†χ^2 statistic for differences between expected frequencies.
‡Sustained-release methylphenidate or dextroamphetamine.

Table 2.—General Feelings of Children Regarding Stimulant Medication

Child's Feelings	No. (%)
Helpfulness of medication	
Very helpful	22 (48.9)
A little helpful	18 (40.0)
Not helpful	5 (11.1)
Child's feelings about medication	
Liked taking medication	15 (33.3)
Neither liked nor disliked medication	20 (44.4)
Disliked medication	10 (22.2)
Would child keep taking medication?	
Every day	21 (46.7)
Some of the time	19 (42.2)
Stop taking medication	5 (11.1)

understanding of why they were receiving the stimulant medication; their attribution of the cause of their problems; the benefits and side effects that they perceived as being due to the stimulant medication; other medication-related complaints or worries; general feelings about its helpfulness; whether they liked, were indifferent to, or disliked taking the stimulant medication; and whether they would continue taking the medication if it was entirely up to them. Children were also asked about their responses to recent media publicity concerning the use of stimulant medication.

Questions were developed through a survey of currently available rating scales for children with ADHD, and the format was based on the ANSER System Self-Administered Student Profile.[14,15] Each child's questionnaire used the name of the child's own medication (methylphenidate hydrochloride [Ritalin] or dextroamphetamine sulfate [Dexedrine])as listed below.

Sample Items From the Children's Questionnaire

1. Before starting Ritalin, I had trouble sitting still in the classroom (circle one):
   a. very true for me
   b. a little true for me
   c. not true for me
2. Now that I am taking Ritalin, I find getting to sleep at night is (circle one):
   a. easier
   b. no different
   c. harder
3. What would you do if you were told that it was entirely up to you whether you took your Ritalin (circle one):
   a. I would keep taking Ritalin every day
   b. I would take it sometimes but not all the time
   c. I would stop taking Ritalin

In addition, the children were asked to complete the Perceived Competence Scale for Children,[16] a self-report questionnaire that measures a child's perception of cognitive, social, and physical competence, as well as general sense of self-worth. Children were asked to complete all questionnaires as independently of parent involvement as possible.

The parents' questionnaire included questions about their children identical to those in the children's questionnaire. In addition, the parents were asked to provide demographic data, stimulant dosage, and medical and developmental histories, including provision of academic and nonacademic support services. Current behavior was described using the Conners' Abbreviated Parent Rating Scale.[17,18]

RESULTS

Demographics

Of the 58 children recruited for the study, both parent and child questionnaires were completed by 45 (77.5%). Table 1 shows that the children who completed the questionnaires did not differ significantly from the children who failed to do so with respect to their age, sex, length of time receiving stimulant medication, or type of medication.

Of those who completed the questionnaires, 36% were receiving standard methylphenidate (mean dose, 16.4 mg/d; range, 5 to 27.5 mg/d; mean dose by weight per day, 0.33 mg/kg per day), 26% were receiving slow-release methylphenidate (mean dose, 23.3 mg/d; range, 20 to 60 mg/d; mean dose by weight per day, 0.53 mg/kg per day), and 38% were receiving dextroamphetamine (mean dose, 12.9 mg/d; range, 10 to 30 mg/d; mean dose by weight per day, 0.28 mg/kg per day); 93% were of middle or upper-middle class socioeconomic background (by Hollingshead's classification[19]); 84% were receiving academic support services at school, 80% were receiving individual or family counseling or psychotherapy, and 38% were involved in a behavior treatment program either at home or at school.

Children's Perceptions

General Feelings.—The majority of children (88.9%) felt that the stimulant medication was helpful to them and most (77.7%) reported that they liked or felt indifferent to taking stimulant medication (Table 2). The vast majority of children (88.9%) also reported that they would keep taking the medication some or all of the time if it were completely up to them.

Attributions.—In general, children had a good understanding of why they were receiving stimulant medication, with a majority of them reporting poor concentration (81.8%) and trouble sitting still in the classroom (71.1%) as reasons for starting the treatment. A significant number of children (31.8%), however, also reported that they did not know why they were receiving stimulant medication, in spite of the fact that all had listed at least two specific reasons (Table 3). Most children (72.7%) attributed their ADHD to physiologic causes ("just something I was born with"), although many children also reported that external factors (schoolwork, teachers, or other students) played a role; a smaller number felt that they were partly to blame for their difficulties ("my fault because I'm lazy") (Table 4).

Medication Effects (Table 5).—The most frequently reported benefits were improved concentration (80%) and improved ability to sit still in the classroom (73.3%). Overall, 97.8% of children reported at least one positive benefit. Many children also reported side effects or other complaints or worries related to the medication. In total, 82.2%

Table 3.—Reasons Given by Parents and Children for Commencing Stimulant Medication

Reasons	Children (n=45), %*	Parents (n=45), %*	% of Agreement†
Poor concentration	81.8	97.7	79.5
Difficulty sitting still	71.1	86.7	66.7
School work too hard	71.1	84.4	82.2
Trouble getting along at home	71.1	80.0	82.2
Poor control of temper	51.1	42.2	73.3
Trouble with friends	48.9	77.8	57.8
Always in trouble at school	43.2	47.7	77.3
Do not know why	31.8	2.3	69.7

*Percentage of children and parents responding "very true" or "a little true" for each reason given. More than one reason could be given for each subject; therefore, percentages do not add up to 100%.

†Percent of agreement between children's and parents' perceptions.

Table 4.—Attributions of Cause of Attention-Deficit Disorder

Cause Attributions	Children (n=45), %*	Parents (n=45), %*	% of Agreement†
Physiologic factors			
"Something I was born with"	72.7	91.3	70.7
"Injury or illness as child"	9.5	16.8	85.4
External factors			
"School work was too hard"	40.9	22.5	68.2
"Other kids caused trouble"	27.3	18.3	75.0
"The teacher didn't like me"	24.4	14.2	82.2
Personal factors			
"My fault because I'm lazy"	22.8	12.2	77.3

*Percentage of children and parents responding "very true" or "a little true" for each attribution. More than one attribution could be given by each subject; therefore, percentages do not add up to 100%.

†Percent of agreement between children's and parents' perceptions.

Table 5.—Perceived Effects of Medication Noted by Children and Parents

Effects of Medication	Children (n=45), %*	Parents (n=45), %*	% of Agreement†
Benefits of medication			
Improved concentration	80.0	97.8	82.2
Better able to sit still	73.3	86.7	73.3
School work easier	58.1	69.8	69.8
Less time in trouble	51.1	51.1	64.4
Better control of temper	44.4	46.7	75.5
Get along better with friends	29.5	47.7	59.1
Get along better at home	37.2	39.5	55.8
Side effects of medication			
Harder getting to sleep	31.0	28.6	71.1
Decreased appetite	31.0	28.6	78.6
Less energy	17.8	13.3	86.7
Sad more often	11.6	14.0	83.7
Increased nervousness	11.6	11.6	90.9
New onset of tics/twitches	4.6	2.3	97.6
Other complaints or worries			
Child feels "different"	48.9	62.2	51.1
Feels "something must be wrong with me"	44.4	60.0	57.8
Worried about long-term effect	35.6	13.3	68.9
Feels "not in control"	26.7	22.2	64.4
Embarrassed about medication	26.7	40.0	64.4
Kids tease about medication	11.1	11.1	91.1

*Percentage of children and parents who noted each effect. More than one effect could be noted for each subject; therefore, percentages do not add up to 100%.

†Percent of agreement between children's and parents' perceptions.

of children reported at least one negative aspect of receiving medication. The most commonly reported side effects were difficulty getting to sleep and decreased appetite.

Adverse Media Reports.—Only 13 children (28.9%) were aware of adverse media reports about stimulant medication. Of these, only three reported that the media reports had made them feel worse about receiving stimulant medication and 10 children stated that the reports had made no difference to the way they felt.

Agreement Between Children's and Parents' Perceptions

Parents and children tended to agree in identifying the children who disliked receiving stimulant medication (86.7% agreement, Phi coefficient, 0.79) and those who would stop taking medication if it were up to them (88.6% agreement, $\varphi = .80$).

Although the majority of children and parents gave poor concentration and trouble sitting still as reasons for commencing stimulant medication, children's and parents' responses differed somewhat (Table 3). Children were less likely than their parents to report poor concentration, trouble sitting still in the classroom, and trouble getting along with friends as reasons for commencing stimulant medication and were more likely to report that they did not know why they were receiving medication. While the majority of children and parents attributed the child's ADHD to physiologic factors (Table 4), a greater number of children than parents attributed their problems to external causes. Although there was reasonable agreement between parents and children regarding the major benefits (improved concentration) and specific side effects (sleep, appetite, etc; Table 5), there was less agreement about more abstract effects such as ability to get along at home or with peers, and feeling "different" or "not in control" while receiving the medication.

Factors Related to Children's Attitudes Regarding Stimulant Medication

Comparisons between children who disliked receiving stimulant medication and those who were not averse to the treatment showed no significant differences in respect to (1) the age of the child, (2) the duration of medication, (3) the presence of other support services, (4) parental occupation or education, (5) the child's awareness of recent adverse newspaper reports regarding stimulant medication, or (6) the child's self-esteem as measured on the Perceived Competence Scale for Children.

A number of factors were found to be related to whether a child would continue taking the stimulant medication if given a choice (Table 6). The five children who said they would stop taking the medication disliked taking it, were more likely to find it unhelpful, were taking standard

Table 6.—Factors Related to Children Who Would Stop Taking Stimulant Medication

Factors	Would Continue Medication	Would Cease Medication	P
Attitude to medication (No. [%])			
Like/indifferent to medication	35 (87.5)	0	<.001*
Dislike receiving medication	5 (12.5)	5 (100)	<.001
Perceived helpfulness of medication (No. [%])			
Helpful	38 (95)	2 (40)	. . .
Unhelpful	2 (5)	3 (60)	<.001*
Type of medication (No. [%])			
Standard methylphenidate†	12 (30)	5 (100)	. . .
Sustained-release medication	28 (70)	0	.002*
Medication dose, mg/kg per day (mean ± SD)			
Standard methylphenidate	0.33 ± 0.16	0.28 ± 0.11	NS
Slow-release methylphenidate	0.52 ± 0.18	. . .	. . .
Slow-release dextroamphetamine	0.32 ± 0.11	. . .	. . .
Conners' Abbreviated Parent Rating Scale Score (mean ± SD)	19.8 ± 5.8	28.4 ± 4.2	.003‡

*χ^2 statistic.
†Sustained-release methylphenidate or dextroamphetamine.
‡Two-tailed *t* test.

methylphenidate, and were more likely to receive a score on the Conners Abbreviated Parent Rating Scale indicating activity and attentional problems while receiving medication. There was no significant difference in the dose per kilogram of methylphenidate prescribed to children who would stop taking stimulant medication compared with those who would continue taking stimulant medication, although the dose per kilogram of standard methylphenidate was relatively low for both these groups of children.

To examine the factors that influence a child's attitude toward receiving medication, we used a logistic regression model in which liking vs disliking medication was predicted by its perceived positive and negative effects on the children. These analyses employed a backward stepwise procedure in which all variables measuring the perceived effects of the medication were entered into the model on an initial step; those failing to contribute significantly to the accuracy of prediction were removed on subsequent steps. Preliminary analyses were performed separately on variables measuring children's and parents' perceptions. In each case, the analyses revealed two variables exhibiting unique and significant relationships with feelings toward receiving stimulant medication. The significant children's variables were a perception that the medication makes them feel as if something is wrong with them ($P = .038$) and feelings of embarrassment about receiving the medication ($P = .029$). The significant parent variables also included a perception that the children who disliked medication were embarrassed about taking it ($P = .042$) and that these children also had more difficulty getting to sleep at night ($P = .015$).

On a subsequent analysis, these four variables, as well as a number of covariates including age, type of medication, and the Abbreviated Conners' scores, were entered into a similar logistic model. Here, only the two parent variables (embarrassment and sleep difficulties) remained statistically significant. However, the type of medication being taken by the child was also marginally significant, with children who disliked taking medication more often taking standard methylphenidate than long-acting stimulant medication ($P = .060$). A model that includes these three variables (embarrassment, sleep difficulties, and type of medication) was able to predict whether a child liked or disliked taking medication, with an overall accuracy of 88.9%, a sensitivity of 97.1%, and a specificity of 60%.

COMMENT

These results show that the majority of children with ADHD who received stimulant medication for more than 6 months as part of a multimodal approach to therapy found the stimulant medication helpful. In contrast to previous studies,[2,3] we found that the majority of children (77.8%) reported that they liked or were indifferent to receiving the medication.

The high rate of acceptance of stimulant medication by children in this study may have been due to a number of factors, including the multimodal approach to the treatment of these children in which education of the child regarding his or her problems is stressed; flexibility of medical treatment regimens so that the type of medication could be more closely tailored to the child's needs; a higher percentage of children receiving long-acting stimulant medication than in previous studies; and the fact that all children in this study were receiving stimulant medication and had been for at least 6 months. Other factors that may have influenced the level of reported acceptance include: (1) possible sampling bias in the group of children who completed the questionnaire compared with those who did not (although the high rate of returned questionnaires and demographic similarities between the two groups makes this less likely); (2) association of the study team with the clinic team; and (3) the forced choice format of the questionnaire.

Although children and parents generally agreed in identifying children who disliked receiving stimulant medication, there was somewhat less agreement in identifying the specific reasons for commencing the medication and in assessing its benefits and adverse effects. Many of these children have been receiving stimulant medication for a number of years, and it is likely that they do not have a

ar recollection of why they started receiving it. In ad-
ion, problems for which such medication is often pre-
ibed involved concepts such as concentration, atten-
n, and relationships with others, which are relatively
stract and may be difficult for many of the children to
ly grasp. Agreement concerning positive and negative
ects was greatest over major benefits (improved con-
tration) and concrete side effects that were evident at
me as well as at school. There was less agreement over
re subjective or abstract concepts, such as ability to get
with others and feeling "different" or "not in control"
ile receiving the stimulant medication. These findings
consistent with those of previous studies[20] concerning
e correlation between parent and child reports. Differing
rceptions may be due to lack of knowledge by the par-
ts about how the child is performing at school, a true
fference of opinions between parents and children, or
e child's cognitive limitations in handling more abstract
estions.

These differences between parents' and children's per-
ectives illustrate the importance of asking children
out their perceptions. The child may express concerns
worries about which the parent is unaware, and which
ay be important in providing a successful treatment reg-
en.

Our findings suggest that children's negative attitudes
ward stimulant medication are often due to a perception
adverse effects or lack of effectiveness. Although all of
ese children had been reported by their parents and
achers to be responsive to stimulant medication, they
ere all receiving a relatively low total daily dose of
ethylphenidate (mean, 0.28 mg/kg per day). It is possible
at this may account for the persistent symptomatic be-
avior among the children and may explain their percep-
ons that the medication was not helpful.[21,22] This sug-
sts that children's reports may provide information
eful in evaluating the potential benefits of changing ei-
er the dosage or type of medication.

The fact that all of the children who would have stopped
king stimulant medication if they could were taking stan-
ard methylphenidate rather than a sustained-release
reparation suggests that the need to take stimulant med-
ation while at school may be an important factor in the
hild's attitude or that sustained-release medication may
e more effective than standard methylphenidate.[23] Pre-
ious studies[24] have shown that compliance for prescribed
erapies can be improved by decreasing the complexity
r inconvenience of the therapy regimen. The need to take
timulant medication at school not only adds to the com-
lexity of the drug regimen, but also increases the like-
hood of embarrassment on the part of the child. Taken
gether, these factors may contribute to the child's dislike
f the medication and decreased compliance.

The findings of this study emphasize the importance of
sking children how they feel about receiving stimulant
edication and of employing a flexible approach that
atches medication regimens to the needs of the children.

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Capillary Refilling (Skin Turgor) in the Assessment of Dehydration

Jose M. Saavedra, MD; Glenn D. Harris, MD; Song Li, MD; Laurence Finberg, MD

This study was undertaken to evaluate the usefulness of kin turgor or capillary refilling in estimating the degree of ehydration in infants with diarrhea. After initial standard:ation of the technique, capillary filling time was found to e more reproducible when measured in the fingernail bed fter applying just the amount of pressure necessary to lanch the nail bed. Capillary refilling time in 30 normal fants 2 to 24 months of age was 0.81±0.31 seconds. Caplary filling time was then measured in 32 infants with dirrhea admitted to the hospital and correlated to the degree f dehydration as estimated from the difference in weight om the time of hospital admission to the weight after reydration. A turgor time of 1.5 seconds or less was found be indicative of a less than 50-mL/kg deficit or of a normal fant; 1.5 to 3.0 seconds suggests a deficit between 50 and 0 mL/kg, and more than 3 seconds suggests a deficit of ore than 100 mL/kg.

(*AJDC*. 1991;145:296-298)

he decrease of skin *elasticity* (the delayed return of skin to its original state after it is pinched into folds) and the ss of skin *turgor* or increased capillary refilling time (the ow return of color to the skin after pressure has been plied) are signs commonly used by pediatricians in the aluation of dehydration, particularly in infants younger an 2 years.[1,2] For many years, one of us (L.F.) has used rgor times learned during his residency; however, to our owledge, no studies have standardized the technique timing skin turgor or evaluating its accuracy as a prector of the degree of dehydration in infants. Accordgly, we set out to obtain data correlating the state of dration in infants by timing capillary refilling.

MATERIALS AND METHODS

Study 1

tudy 1 was performed to standardize the technique of mearement of capillary refilling (turgor time). Three different obvers used a stopwatch to time the capillary refilling in three rmal infants 6, 9, and 14 months of age, at two different sites il bed and heel), on three separate occasions, a total of six times r patient per observer per site.

o measure capillary refilling time in each instance, the obver applied pressure with his right thumb at the site chosen: nail bed of the right thumb or the right heel. Also, in each instance the measurement was made with two "degrees" of pressure applied: one degree of pressure was enough only to blanch the site ("light") and the other was "moderate" pressure. The pressure was maintained for 1 to 2 seconds and the capillary refilling was timed with a stopwatch from the moment of release to total recovery of color of the blanched area. Occasionally, a second person was necessary to gently immobilize the child's limb.

The types of measurements performed included nail bed with light pressure applied, nail bed with moderate pressure applied, heel with light pressure applied, and heel with moderate pressure applied. The times thus obtained were compared among observers, subjects, degrees of pressure applied, and sites.

Additionally, one of the investigators measured the nail bed refilling time applying light pressure in 30 apparently healthy infants seen in an outpatient clinic for a routine "well child" visit and immunization. The only criterion for selection was that they had had no apparent illness for the last 2 weeks prior to the visit.

Study 2

Study 2 was performed to evaluate capillary refilling (turgor time) as an estimate of the degree of dehydration. Any patient admitted to the infant ward at Kings County Hospital, Brooklyn, NY, with a history of diarrhea, with or without clinical evidence of dehydration, was enrolled in the study.

On admission to the ward and at regular intervals (usually after 4, 12, and 24 hours, and twice daily thereafter), the patients' conditions were reassessed for their hydration status. Weight and capillary refilling time were determined simultaneously at the time of admission to the ward. Particular attention was given to weighing the patients accurately. Infants were weighed on a digital scale, without clothes or diapers, and possible sources of error were accounted for (eg, intravenous equipment, armboards, etc).

Given the results in study 1, detailed below, capillary refill times were measured in the nail bed with light pressure applied. The times measured in the heel were not considered. The degree of dehydration of the patients (in milliliters per kilogram of body weight) was determined by the difference in weight from the time of hospital admission to "stable weight" once the infant had no clinical signs of dehydration. Stable weight was defined as the mean of two consecutive daily weights with a difference no greater than 2% of the highest of these two weights. The extent of dehydration thus calculated was correlated with the capillary refilling time at the time of hospital admission.

RESULTS

Study 1

Figure 1 shows the capillary refilling times found in three healthy, well-hydrated infants by three different observers. There were six observations per patient per observer for a total of 54 measurements per site per degree of pressure applied (nail bed with light pressure, nail bed with moderate pressure, heel with light pressure, and heel

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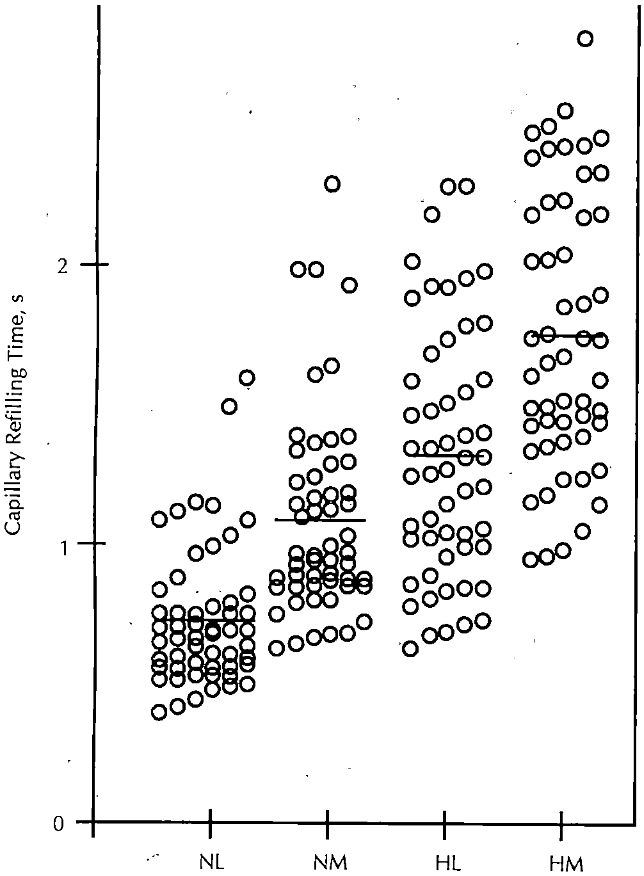
rom the Department of Pediatrics, SUNY Health Science Center rooklyn (NY).

eprint requests to Box 49, 450 Clarkson Ave, Brooklyn, NY 11203 Finberg).



	NL	NM	HL	HM
Mean	0.73	1.09	1.32	1.76
±SD	±0.25	±0.37	±0.45	±0.49

Fig 1.— *Scattergram of 54 measurements of capillary refilling time (turgor time) in three normal infants in two sites and applying two degrees of pressure: "light," just enough to produce blanching and "moderate" pressure. NL indicates fingernail bed with light pressure applied; NM, fingernail bed with moderate pressue applied; HL, heel with light pressure applied; and HM, heel with moderate pressure applied. Measurement of capillary filling in the nail bed using light pressure was the most reproducible.*

with moderate pressure). The means and SDs for turgor time in each site with different pressure applied are shown. The shortest times were obtained in the nail bed of the hand; the longest times were obtained in the heel. In both sites, an increase in the amount of pressure applied, moderate vs light, prolonged turgor time. The least scatter with the smallest SD was also smaller in the nail bed as compared with the heel. For this reason, refilling time measured in the nail bed applying light pressure was the technique used in study 2. For the three observers who participated in the study, the interobserver coefficients of variation for 54 measurements done on three separate occasions were 28%, 36%, and 25%, and the intraobserver coefficients of variation in the same opportunities were 25%, 35%, and 32%.

Using the same technique, 30 healthy infants had their conditions evaluated. Their median age was 6 months, with a range of 2 to 24 months. Fifteen were male and 15 were female. Refilling time in this group was 0.81±0.31 seconds.

Study 2

A total of 32 patients (16 male and 16 female infants) were studied. Median age was 6 months, with a range from 1 week to 26 months.

Figure 2 shows the correlation of the refilling times at hospital admission with degree of dehydration. Of the 24 patients with a deficit greater than 50 mL/kg, only one

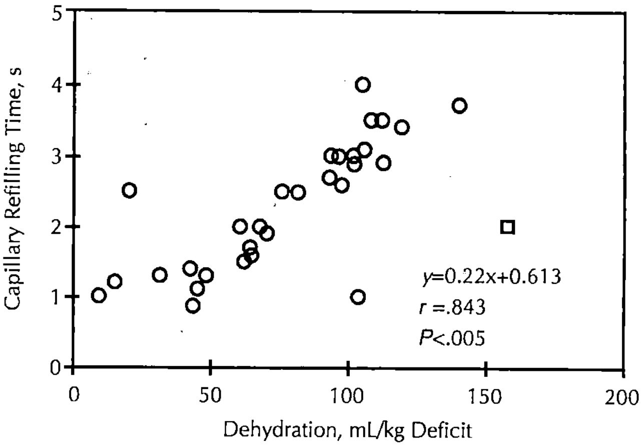


Fig 2.—*Correlation of capillary refilling time and degree of dehydration at the time of admission to the hospital. A square was not used in the regression analysis.*

(4.2%) had a refilling time of less than 1.5 seconds. Only one (11.1%) of nine patients with a refilling time of less than 1.5 seconds had a deficit greater than 50 mL/kg. Thirteen (76.5%) of 17 patients with a refilling time between 1.5 and 3 seconds had deficits between 50 and 100 mL/kg. Of the 11 patients with more than 100 mL/kg of deficit, 10 (90.9%) had refilling times greater than 1.5 seconds and seven (63.6%) had refilling times greater than 3.0 seconds. The correlation coefficient of .843 was significant ($P<.005$).

COMMENT

Skin turgor (capillary refilling) and skin elasticity are useful clinical signs in the assessment of dehydration.[1] Unfortunately, the terms have been used interchangeably in the literature leading to considerable confusion.

Elasticity is the physical property a body has to return to an original shape after it has been compressed, bent, or otherwise distorted. Thus, skin elasticity is the characteristic of the skin to spring back to its original shape after a fold of skin has been pinched up.[3-7] The loss of elasticity is also referred to as "tenting." The term *turgor*, on the other hand, refers to the fullness or resiliency of living animal or plant cells, and *turgor vitalis* refers to the normal fullness of the blood vessels or capillaries. It is preferable, then, to reserve the use of the term *skin turgor* to allude to the filling of the vascular bed of the skin. Turgor time is commonly referred to as *capillary refilling time*, the term we have chosen to use herein to avoid confusion.

Many sources use the terms *turgor* and *elasticity* interchangeably,[8,9] and others advocate the use of only skin elasticity in the clinical assessment of dehydration.[10,11] Laron and Crawford[12] showed a significant correlation between dehydration and skin elasticity (which they called turgor) as measured by timing the return of a pinched skin fold to its original contour. A time of 0.5 seconds was found with a weight loss of 2.5% to 5% and a time of 1 to 2.5 seconds was found with a weight loss of 5% to 8% in infants with diarrhea. Skin elasticity, while altered in dehydrated patients, can be affected significantly in the presence of malnutrition, obesity, or edema.

The presence of skin turgor is a sign of circulatory adequacy, since the speed of refilling of the capillary bed is responsible for the rapid return of color of the skin after the area has been blanched by pressure. The time for this refilling can be influenced by a number of factors, including the site, presence of edema, characteristics of the skin, temperature, and cardiovascular status. The nail bed, the thenar surface, and the heel are the usual preferred sites, particularly in dark-skinned infants. Our results suggest that between the fingernail bed and the heel, the former is better, because the color is more readily seen and reproducibility is better.

The presence of the glomus body, a highly organized arteriovenular anastomosis found under the nail bed, offers a practically direct visualization of the peripheral vascular bed. The glomus bodies are richly innervated with sympathetic fibers. Theoretically then, nail bed capillary refilling time is not only related to the actual intravascular volume but is also a sensitive reflection of the compensatory mechanisms that come into play in the peripheral circulation (vasoconstriction) during states of dehydration.

The amount of pressure applied makes a difference. Obviously, the amount of pressure is subjective, but it would not be practical to standardize it using mechanical devices. From our findings it appears that applying the minimal pressure necessary to produce blanching will yield more reproducible measurements. We did not assess the effect of maintaining the pressure for different periods before releasing, although probably the shorter time in which this is done, the less variability will be introduced. Timing can be done with a simple and usually inexpensive stopwatch, but with practice these times can be reasonably estimated without the need of a watch.

The average refilling time obtained in the nail bed in the normal infants studied was 0.81±0.31 seconds. This would imply that refilling time in normal children can be expected to be as high as 1.43 seconds (mean+2 SDs) or 1.5 seconds for practical purposes. This is in agreement with the fact that in study 2 refilling time was 1.3±0.5 seconds in the children with diarrhea but with a deficit of less than 50 mL/kg. The values for normal infants are also close to those of Schriger and Baraff[13] who reported an average capillary refilling time of 0.9±0.5 seconds using the pulp of the distal phalanx in children 1 month to 12 years old. In adults, the average increased to 1.3±0.7 seconds. From our measurements also, refilling time in the heel could be as high as 2.7 seconds in normal infants without any fluid deficit.

Capillary refill time correlated well with the degree of dehydration of the patients admitted to the hospital for diarrhea. It is apparent that a refilling time of 1.5 seconds or less is indicative of a less than 50-mL/kg deficit or of a normal infant; a refilling time of 1.5 to 3.0 seconds suggests a deficit between 50 and 100 mL/kg, and a refilling time greater than 3 seconds suggests a deficit of more than 100 mL/kg.

Certain clinical situations not evaluated in this study could alter capillary filling time. Hypothermia, hyponatremia, and cardiac failure may prolong it. Fever may have the opposite effect, and hypernatremic states clearly do so. Similarly, hypernatremia appears to preserve skin elasticity to a certain degree in the presence of dehydration.[14] The clinician must bear both of these complications in mind when making a quantitative judgment. The influence of nutritional status on capillary refilling time was not assessed in this study. In our experience, a marasmic state would not affect the results unless complicated by cardiac malfunction. In the presence of edema (kwashiorkor), capillary filling times might be less reliable.

In conclusion, capillary refilling time measured in the fingernail bed (preferred site) is a valuable technique in estimating the degree of dehydration and should be part of the clinical assessment of an infant's hydration status. A value less than 1.5 seconds in the fingernail bed, applying only the pressure necessary to blanch it, suggests a normal hydration status or a deficit of less than 50 mL/kg. A time of 1.5 to less than 3 seconds suggests a deficit of 50 to 100 mL/kg, and a time of greater than 3 seconds suggests a deficit of 100 mL/kg or more.

In clinical settings, with a little experience and without a stopwatch, one can ascertain the following hydration status: if less than 2 seconds, minimal or no dehydration; if between 2 and 3 seconds, a 50- to 100-mL/kg deficit; if between 3 and 4 seconds, a 100- to 120-mL/kg deficit; and if more than 4 seconds, a greater than 150-mL/kg deficit and urgent danger. As with all clinical signs, even with one as useful as this, there will be occasional variants that usually can be anticipated by the patient's overall condition and the environmental circumstance in which he or she is found.

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Practice Management Training for Pediatric Residents

Janice P. Piatt, MD; Douglas L. Bartley, MD; Albert D. Jacobson, MD; Mary E. Rimsza, MD

• In 1986, a practice management training program was developed for pediatric house staff. In conjunction with this program, pediatric residents for the following 2 years completed questionnaires regarding their career goals, interests, and perceived competence in practice management. Postgraduate level–3 residents who completed the program felt more competent than postgraduate level–1 residents in all areas of practice management and were more likely to take an active role in managing their practice. There was a significant difference between postgraduate level–1 and level–3 residents who completed the program in several areas: feelings of overall competence in office management, choosing a practice location, office staff, appointment system, billing system, office computer, fee schedules, telephone management, and setting up an office laboratory. Exposure to a practice management program during residency training may better prepare future pediatricians for a successful practice.

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The clinical practice of medicine continues to become more complex with expanding technology and increasing specialization. The business aspects of practice are also becoming more demanding, with tighter regulations, third-party restrictions, and increasing litigation.

Although most pediatric residents will ultimately work in a private practice after completion of their training, they are rarely exposed to the issues that are important in managing a practice. To meet these needs, an educational program was designed to provide residents with training in practice management.

In April 1986, one of us (A.D.J.) attended a meeting sponsored by the American Academy of Pediatrics (AAP) on practice management training for residents. Following this meeting, a faculty curriculum committee was established and the practice management program was initiated in October 1986. The goals of the program were as follows: (1) to familiarize pediatric residents with different types of office settings, including small and large group private practices, closed-panel health maintenance organizations (HMOs), and private pediatric subspecialty practices; (2) to increase residents' knowledge and thus feelings of competence in managing a practice; (3) to increase residents' knowledge and thus competence in establishing their own practices; and (4) to provide residents with practical information on private practice experiences that can aid them in establishing their own career goals.

Our program relied heavily on the guidelines set forth by the Committee on Practice and Ambulatory Medicine of the AAP. This committee produced a manual on practice management and developed a sample course outline using both didactic lectures and office preceptorships. The committee believed that the major objectives of a practice management program should be to familiarize pediatric trainees with the major issues in practice management, to provide an opportunity for the trainee to observe the mechanics of practice management in an office setting, and "to observe the unique relationship between practitioner and patient in the private office setting and discover how this relationship influences the context of practice."[1]

At the beginning of the program, the residents were asked to complete a questionnaire regarding their career goals, interest in practice management, and perceived competence in various aspects of practice management. The questionnaire was repeated at the completion of each academic year for the next 2 years. The purpose of the questionnaire was to try to evaluate how career goals and attitudes about practice management change from postgraduate level (PL)–1 to PL-3. We also were interested in evaluating whether PL-3 residents who had participated in the practice management program felt more competent in establishing and managing a practice than the PL-1 residents. This report discusses the practice management

Department Editors.—*Hugh D. Allen, MD, Columbus, Ohio; Fredric Burg, MD, Philadelphia, Pa; Harold Levine, MPA, Galveston, Tex; Barbara Starfield, MD, Baltimore, Md; Larrie W. Greenberg, MD, Washington, DC*

Purpose.—*This department is intended to share information concerning educational efforts in the broad field of pediatrics. We welcome studies on the following topics: undergraduate and graduate education in medicine and allied health occupations; continuing education of health professionals; education of patients and families; and health education for the general public, the community, and organizations that contribute to the promotion and improvement of the health of children.*

Editorial Comment.—*During their training, we spend several months teaching our residents how to adjust ventilators in the neonatal intensive care unit, a technique they are then permitted to watch after residency as practitioners at the same hospital. At the same time, do we teach them how to run their practice, a real and necessary skill? This article describes a successful practice management training program that may have importance for your training programs.*—H.D.A.

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From the Departments of Pediatrics, Maricopa Medical Center, Phoenix, Ariz (Drs Bartley and Rimsza), and Phoenix Children's Hospital (Dr Piatt). Dr Jacobson is in private practice in Phoenix.

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Reprint requests to Department of Pediatrics, Maricopa Medical Center, PO Box 5099, Phoenix, AZ 85010 (Dr Rimsza).

program used in our residency program and the results of the practice management questionnaire that was completed by the house staff.

DESCRIPTION OF PROGRAM

The practice management program was developed by a private practitioner (A.D.J.) and full-time faculty member (M.E.R.) based on the recommendations of the AAP Committee on Practice Management and Ambulatory Care. The program consisted of didactic lectures and office preceptorships. Six didactic lectures on practice management topics were added to the core curriculum lecture series for residents. Topics for these lectures included "Insurance," "Selecting Accountants/Attorneys," "Practice Location," "Types of Practice (HMO or Small Group)," and "Personnel Management." Additionally, arrangements were made for outside experts on practice management to provide two half-day seminars for our house staff biannually.

The most important part of the program was the office preceptorship. Five pediatric offices that represented different types of practice experiences as listed below were asked to participate. An outline of areas to be covered during each session was given to the participating private pediatrician.

- Small group practice 1
  - Introduction to small group practice
  - Marketing and satellite office
  - Printed materials
  - Current procedural terminology codes, medical records
  - Telephone management
- Small group practice 2
  - Laboratory
  - Fees and compensation
  - Financial planning
  - Professional courtesy
- Large primary-care group
  - Introduction to large group practice
  - Office personnel
  - Accounting, legal, and management services
  - Time conservation and peer and community relations
- HMO
  - Introduction to HMOs
  - Office equipment
  - Computers in practice
  - Appointment system
- Subspecialty practice
  - Introduction to subspecialty practice
  - Fees and compensation
  - Risk management
  - Business office and payment systems

Each resident was assigned to spend one half-day per week in each practice management office preceptorship during five 1-month elective rotations. This program was offered to second- and third-year pediatric residents. Four PL-3 chief residents each year did not participate. Since our PL-2 and PL-3 residents normally have three elective experiences per year, they completed the entire practice management program by the completion of their third year of residency. Most preceptors had residents assigned to them for 30 half-day sessions per year. The residents' reading assignments for the course included the AAP's *Management of Pediatric Practice*[1] and other materials provided by the participating private practitioners and lecturers. Each office designed its own program using specific guidelines. The sessions usually began with an office tour and discussion about the assigned topics prior to regular office hours. Most offices involved their business managers and office staff in the teaching program as well. The residency program was unable to directly reimburse the participating pediatricians for their teaching efforts, but did make arrangements for these physicians to attend our hospital-sponsored continuing medical education programs without charge.

METHODS

At the start of the program, and for the next 2 years, incoming PL-1 residents completed a questionnaire regarding their career goals, interests, perceived competence, and knowledge of various aspects of practice management. This questionnaire was also administered to third year (PL-3) residents who had participated in the practice management curricula at the end of their PL-3 year in 1987 and 1988.

Comparison of Responses to Questions of Perceived Competence by PL-1 Residents vs PL-3 Residents*

Perceived Competence in:	PL-1	PL-3	$P<$
Office management	2.45	4.80	.0001
Selecting a practice location	2.97	6.00	.0001
Designing an office	2.98	4.53	.006
Choosing office staff	3.15	5.13	.001
Choosing appointment system	1.96	4.80	.0001
Choosing billing system	1.66	4.46	.0001
Selecting a computer system	1.72	3.93	.0001
Telephone management	2.42	5.46	.0001
Setting up fees	2.30	4.93	.0001
Setting up laboratory	2.27	4.93	.0001

*Residents were asked to rate their feelings of competence on a scale of 1 (no competence) to 9 (very competent). Values are means. PL indicates postgraduate level.

RESULTS

Thirty-four (85%) of 40 PL-1 residents and 15 (83%) of 18 eligible PL-3 residents completed the questionnaire. Most PL-1 residents (56%) expected to enter a subspecialty area of pediatrics. However, 86% of the PL-3 residents planned to enter general pediatrics and only 7% chose a subspecialty. (The percentages do not add up to 100 because some residents did not complete the question or did not know their preference.)

Residents were asked to indicate what type of practice they preferred (private, academic, HMO, hospital-based, or unknown). The majority (85%) of the PL-3 residents preferred to work in a private practice setting, usually in a small group. Thirty percent of the PL-1 residents also chose private practice, but 35% did not know what type of practice they preferred. Residents were asked the following question:

I prefer to have the business aspects of my practice handled by

(a) a partner;
(b) a business manager;
(c) me;
(d) an institution that employs me.

The majority of the PL-1 and PL-3 residents preferred to use the services of a business manager. No resident wanted his or her partner to run the office and only one resident chose an institution. Only 15% of the PL-1 residents wanted to manage the office themselves, while 33% of the PL-3 residents wanted to manage their own offices or use their own skills in addition to a manager.

The questionnaire also asked residents to select the type of practice they thought would provide the easiest call schedule. Sixty-five percent of the PL-1 house staff thought the call schedule would be easiest for them in an HMO. Twenty-one percent chose a hospital-based practice and 12% chose private practice. However, 44% of the PL-3 residents believed that their call would be easiest in a private group practice and 38% felt it would be easiest in an HMO.

The residents were also asked to rate the importance of call schedule, patient population, and problems managing the business aspects of practice in their decisions about choice of practice. Seventy-six percent of the PL-1 residents and 80% of the PL-3 residents rated the type of patient they would see as important in their decision. Forty-seven percent of the PL-1 residents and 33% of the PL-3 residents thought the call schedule was important. Forty-one percent of the PL-1 residents believed that their choice of practice would be based on their *dislike* for handling the business aspects, and only 6% believed that their choice would be based on the fact that they *enjoyed* managing the business aspects of practice. In contrast, only three PL-3 residents (20%) believed that their choice of type of practice would be based on their *dislike* for handling the business aspects of practice and 20% felt that their choice would be based on their enjoyment of handling the business aspects of practice. (These numbers are greater than the number of respondents, since residents were asked to circle all answers that applied.)

Residents were asked to rate their feelings of competence in practice management issues in a series of questions using a scale of 1 to 9, with 1 representing a low competence and 9 a high competence. The results were analyzed statistically using Student's *t* test on a computerized software program (Table). There was a statistically significant difference between PL-1 and PL-3 residents who had completed the practice management course in the following areas: perceived competence in office management, choosing a practice location, office design, choosing office staff, appointment systems, billing systems, computer systems, and deciding fee schedules. There was also a statistically significant difference between PL-1 and PL-3 residents' confidence in telephone management and setting up an office laboratory. There was no significant difference between PL-1 and PL-3 residents' level of interest in practice management issues, perceived relevance of a practice management course, or desire to learn more about practice management (average scores, 6.5 to 8.0).

The PL-3 residents were also asked to evaluate the program. Comments were generally quite favorable. Residents found the sessions with office managers and the discussions with private practitioners to be especially useful. The only complaint about the program was that the practice management sessions were taken out of elective time. Most residents would have preferred to have the practice management experience as part of other rotations. The practice management experience has now been moved to a third-year clinic rotation. Residents may also elect to spend time in practice management during ambulatory electives as well. The office preceptors in general enjoyed working with our house staff.

COMMENT

The PL-3 residents who participated in our practice management program felt more competent in all areas of practice management than the PL-1 residents. Perhaps because of this greater sense of competence, 33% of the PL-3 residents were planning to take an active role in managing the business aspects of their practice.

Despite a large number of PL-1 residents (56%) who expected to practice a subspecialty, most of our PL-3 residents had opted for general pediatrics by the completion of their third year of residency. During the past 13 years, approximately 26% (similar to the national average)[2] of our residents have continued their training in either a pediatric subspecialty or other residency after their PL-3 year. Thus, the number of residents (86%) entering general pediatric practice immediately after the PL-3 year during the study period was slightly high for our program.

It is possible that the practice management experience influenced our pediatric residents to choose a career in general pediatrics over a subspecialty, but without the benefit of a "control" group of PL-3 residents who had not participated in practice management and completed their residencies during the same academic year, this question could not be answered. Perhaps some residents enter fellowship training because they are fearful of starting a practice and thus wish to defer assuming this responsibility until a later date by working in a hospital or university setting.

We suspect that the change in our resident's perception of call schedule differences was directly related to their practice management experience. Again, however, this change, may be unique to our community and may relate to the call schedules of the private practitioners who participated in our practice management program. None of the reference materials we provided, including the AAP guidebook *Management of Pediatric Practice*,[1] discussed the types of practice that had the easiest call schedules.

A practice management program can easily be incorporated into pediatric residency training with the help of community pediatricians. Previous authors have shown that office pediatric rotations are helpful in reducing misconceptions about private practice and can be beneficial to both the resident and the practitioner.[3-5] Residents are very interested in learning more about practice management and developing skills that will be essential to their success in the private community. In addition, knowledge about practice management issues "can lower the business stresses a physician faces, permitting them to devote more energy to the practice of medicine."[3] Therefore, pediatric training programs should consider adding practice management lectures and experiences to residency training.

We would like to thank the following physicians and their office staff for their help in making the practice management program possible: Richard S. Reznick, MD, and associates; Mary McGee, MD, and associates; Howard S. Kandell, MD, and associates; Robert Hellmers, MD, and associates; and Jesse Cohen, MD, and associates.

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Article

Neonatal Hepatitis and Extrahepatic Biliary Atresia Associated With Cytomegalovirus Infection in Twins

Michael H. Hart, MD; Stuart S. Kaufman, MD; Jon A. Vanderhoof, MD; Steven Erdman, MD; James Linder, MD; Rodney S. Markin, MD; Robert Kruger, MD; Dean L. Antonson, MD

• Prenatally acquired cytomegalovirus infection in twins was temporally associated with a discordant development of neonatal hepatitis and extrahepatic biliary atresia. This case presents evidence suggesting an association between perinatal cytomegalovirus infection and selected extrahepatic biliary atresia and neonatal hepatitis. Congenital cytomegalovirus infections and cytomegalovirus hepatitis are also discussed.

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Extrahepatic biliary atresia (EHBA) occurs in approximately one of 10 000 live births. It is a disease of unknown origin that has been variably attributed to genetic,[1-4] toxic,[5] or infectious[6-8] causes. Concordance[9] and discordance[5,10-12] of biliary atresia have been described in newborn twins. The variable expression of biliary atresia in these infants supports a multifactorial cause of the pathogenesis of EHBA and Landing's[6] hypothesis that neonatal hepatitis and EHBA are a continuum of the same disease.

Cytomegalovirus (CMV) infection occurs in approximately 1% to 2% of newborns,[13-15] with greater than 90% of infected newborns being asymptomatic.[16] Although CMV infection can cause neonatal hepatitis and has been associated with EHBA,[17-19] a causal relationship with the latter has never been documented. We describe a set of twins with prenatal CMV infection and discordant development of neonatal hepatitis and EHBA. Albeit circumstantial, the data from our report support the concept of neonatal hepatitis and EHBA as different expressions of a similar disease process. This case also supports a possible causal association between CMV infection and the pathogenesis of selected cases of EHBA.

PATIENT REPORTS

Twin A.—Twin A was born after 35 weeks' gestation and weighed 2100 g. He was not identical to his twin, as determined by human leukocyte antigen typing, and had an Apgar score of 6/9 at 1 and 5 minutes. Both twins had normal karyotypes (46,XY). Maternal history included a culture-negative pharyngitis with adenopathy and malaise 4 weeks before delivery. Hyperbilirubinemia was noted in the infant on day 2, when total bilirubin measured 242 μmol/L, and direct bilirubin, 94 μmol/L. A urine culture on day 2 was positive for CMV. γ-Glutamyl transpeptidase measured 748 U/L on day 6 and 596 U/L on day 10. The serum α_1-antitrypsin level was normal, measuring 1.07 g/L. Results of tests for possible infectious and metabolic causes of hepatitis with conjugated hyperbilirubinemia were negative. Abdominal ultrasonography revealed an enlarged liver with a normal-appearing spleen. The gallbladder wall was slightly thickened, and no gallstones were found. The common bile duct appeared normal. Levels of bilirubin (total and direct), aspartate aminotransferase, alanine aminotransferase, and γ-glutamyl transpeptidase were elevated (Table). A urine culture again yielded CMV. A hepatobiliary scan using diisopropylimido acetic acid showed good dye uptake by the liver, with delayed excretion into the gallbladder and bowel. A biopsy of a liver specimen was positive for CMV by viral culturing and immunoperoxidase staining. Microscopic examination of a liver specimen showed expanded portal areas with dense, mixed cellular, inflammatory infiltrate. Some neutrophils had infiltrated ductal epithelium. Bile ducts were present in most portal areas, and only occasional proliferative-appearing ductules were found. The lobule was moderately disorganized, with prominent multinucleated hepatocytes and giant-cell transformation. Trichrome staining showed mild portal fibrosis with portal bridging and fine bands of fibrosis tissue extending into hepatic parenchyma. No regenerative nodules were identified. The patient has done well since, and has had normal, age-appropriate weight gain. At age 1 year, his hepatosplenomegaly had resolved and serum and urine values had normalized (Table).

Twin B.—Twin B, a male, weighed 1890 g and had an Apgar score of 3/6 at 1 and 5 minutes. On day 1, the patient was identified with hemodynamically significant coarctation of the aorta and a tracheoesophageal fistula with esophageal atresia (Gross type C). The coarctation was repaired on day 1 with concomitant placement of a gastrostomy tube. Definitive surgical correction of the tracheoesophageal fistula/esophageal atresia was performed on day 4. On day 2, the infant had hyperbilirubinemia, with a total bilirubin level of of 208 μmol/L and a direct bilirubin level of 64 μmol/L. A culture of urine collected on day 2 yielded CMV. Results of a VDRL test were negative, as were results of titers for herpes, toxoplasmosis, and rubella, and serologic tests for hepatitis A and B. Levels of γ-glutamyl transpeptidase on day 6 were elevated to 396 U/L. Levels of serum α_1-antitrypsin were normal (1.37 g/L) (Table). Abdominal ultrasonography revealed a persistent ductus venosus and nonvisualization of the gallbladder. Liver and spleen were otherwise unremarkable. On day 13, the patient underwent a duodenal duodenostomy secondary to an obstructive annular pancreas. At surgery, a normal-appearing, bile-filled gallbladder was identified, as was a normal-appearing extrahepatic biliary system. Biopsy of a liver specimen revealed several large portal areas showing bile ducts, blood vessels, and

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From the Departments of Pediatrics (Drs Hart, Kaufman, Vanderhoof, Erdman, and Antonson) and Pathology (Drs Linder, Markin, and Kruger), Creighton University School of Medicine, University of Nebraska Medical Center, Omaha.

Reprint requests to the Division of Pediatric Gastroenterology and Nutrition, Creighton University School of Medicine, 601 N 30th St, Omaha, NE 68131 (Dr Hart).

Enzyme Levels in Twins With Extrahepatic Biliary Atresia

Substance	Twin	Day 2	Day 6	Day 10	Day 25	Day 56	Day 73	Day 83	Day 90	Day 150
Aspartate aminotransferase, U/L	A	. . .	. . .	204	. . .	. . .	. . .	. . .	158	129
	B	. . .	. . .	256	. . .	. . .	. . .	. . .	253	192
Alanine aminotransferase, U/L	A	. . .	. . .	145	. . .	. . .	. . .	. . .	176	151
	B	. . .	. . .	176	. . .	. . .	. . .	. . .	135	156
Total bilirubin/direct bilirubin, μmol/L	A	242/94	208/54	174/82	. . .	. . .	. . .	. . .	50/38	8/2
	B	208/64	266/126	166/104	84/70	132/98	140/98	116/86	166/152	128/94
γ-Glutamyl Transpeptidase, U/L	A	. . .	748	596	. . .	. . .	. . .	. . .	761	460
	B	. . .	396	. . .	378	828	1140	1056	1302	1051

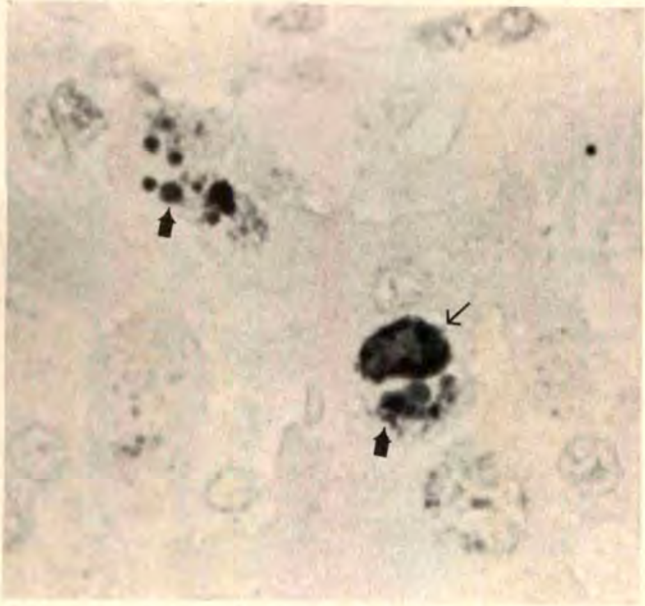

Fig 1.—*Complementary DNA probe of a liver biopsy in twin B shows intranuclear (thin arrow) and intracytoplasmic (wide arrows) staining (original magnification ×400).*

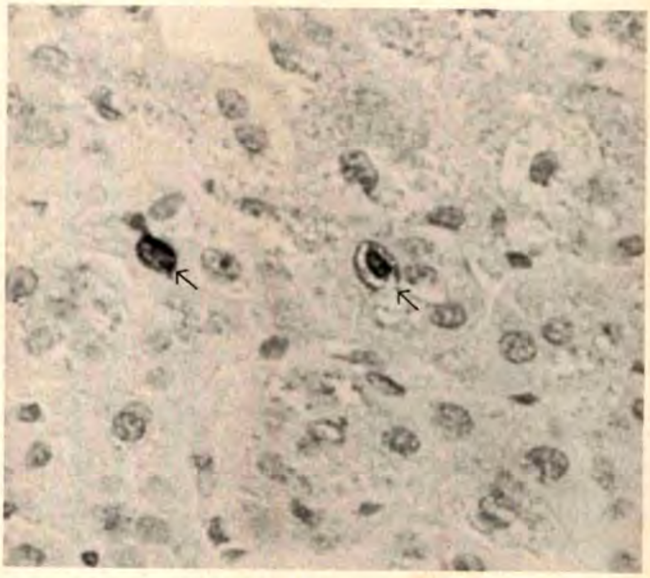

Fig 2.—*Immunoperoxidase stain for cytomegalovirus (arrows) in a liver biopsy specimen of twin B (original magnification ×400).*

focally prominent inflammatory infiltrates of histiocytes and scattered neutrophils. The hepatic parenchyma was moderately disorganized. Hepatocyte cytoplasm showed granular and vacuolar degeneration associated with abundant intracytoplasmic and intracanalicular bile pigment. Gomori's stains showed significant fibrosis extending from portal areas. No cholangiolar proliferation was noted. Bile ducts were adequate, ruling out syndromic paucity of biliary ducts. A complementary-DNA probe for CMV[20] and viral cultures were negative. A hepatobiliary scan using diisopropylimido acetic acid on day 27 showed good dye uptake and no biliary excretion for up to 24 hours. A second liver biopsy was performed on day 29, revealing histologic changes similar to those of the biopsy on day 13. A complementary DNA probe for CMV was positive (Fig 1), as was a CMV-specific immunoperoxidase stain[21] (Fig 2). Exploratory laparotomy was performed on day 42. During surgery, obliteration of a previously normal extrahepatic biliary system was noted, and a fibrous atretic cord was identified in lieu of a common hepatic duct. An operative cholangiogram showed no hepatic radicles. While no dye was initially excreted, follow-up films suggested that dye had passed into the duodenum. A Kasai procedure and liver biopsy were performed. This biopsy showed prominent cholestasis, which was primarily centrolobular and focally panlobular. Hepatocytes, ductules, and Kupffer's cells contained bile. Binucleated hepatocytes were seen occasionally, although giant-cell transformation was not present. Focal collections of neutrophils were present in the lobule without associated necrosis. In contrast to results of a previous biopsy, portal tracts showed variable ductular proliferation, and a trichrome stain indicated periportal fibrosis. Three cystic duct sections showed patent ducts surrounded by smaller ductular structures and mononuclear cells. Bile was not seen in the lumen. The fourth duct showed a smaller, stenosed lumen with epithelial sloughing. Each section taken from the porta hepatis exhibited a compressed cut with considerable sloughing of biliary epithelium. Deeper sections showed multiple smaller branches replacing the larger duct. These structures were surrounded by fibrous tissue and mononuclear cells. The gallbladder lumen did not contain bile. The lining of the epithelium was tall and columnar with some cytoplasmic vacuolization and intracellular bile staining. A complementary DNA probe, an immunoperoxidase stain, and a viral culture were all negative for CMV. Postoperatively, the patient did not have significant bile flow. Bilirubin values at age 2 months remained elevated (Table). At age 4 months, the patient experienced apnea and cyanosis associated with a viral pneumonitis. Cytomegalovirus was cultured from bronchial washings, and intracytoplasmic inclusions were noted in bronchial epithelium cells. Treatment with dihydroxypropylmethyl guanine was initiated. The patient responded to treatment and was in good condition at discharge from the hospital. Because of progressive end-stage liver disease, orthotopic liver transplantation was performed at age 2 years. Pathologic evaluation of the intact liver confirmed previous histologic findings of extrahepatic biliary atresia. Viral cultures, a complementary DNA probe, and an immunoperoxidase stain were negative for CMV at transplantation. At age 7 weeks, both twins tested positive for IgG to CMV (≥1:640; maximal dilution) and negative for IgM to CMV (<1:10). Maternal titers of antibodies to CMV were 1:16 for IgG and nondetectable for IgM.

COMMENT

Before 1974, neonatal hepatitis and EHBA were generally considered separate entities. In 1974, Landing[6] proposed that neonatal hepatitis, EHBA, and choledochal cysts were different expressions of a continuum of "infantile obstructive cholangiopathy." The discordant expression of EHBA and neonatal hepatitis in twins associated in part with CMV infection, as described herein, supports the concept of EHBA and neonatal hepatitis as a continuum of expression of infantile obstructive cholangiopathy.

Cytomegalovirus infection is the most common congenital viral infection. Prevalence rates for congenital CMV infection vary from 0.5% to 2.4% of live births.[13-16] Fewer than 10% of infected infants are symptomatic.[16] Frequent abnormalities associated with symptomatic congenital CMV infection are petechiae (79%), hepatosplenomegaly (74%), jaundice (63%), microencephaly (50%), height and weight below normal for gestational age (41%), prematurity (34%), inguinal hernia (26%), and chorioretinitis (12%).[22] Results of laboratory tests of infected newborns include increased cord IgM (84%), atypical lymphocytosis (80%), elevated aspartate aminotransferase level (79%), thrombocytopenia (61%), and increased cerebrospinal fluid protein (47%).[22] Our patients did have evidence of hepatosplenomegaly and jaundice, although they did not exhibit microencephaly, chorioretinitis, thrombocytopenia, petechiae, or intracranial calcifications. These infants apparently were infected prenatally, most probably 1 month before delivery, when maternal symptoms were noted. In this instance, the classic findings of congenital CMV infection would not necessarily be present. Twin B did have other congenital anomalies that were not attributed to CMV infection. In all likelihood, the other congenital anomalies were merely coincidental, although their presence and the clinical course that ensued may have modified the host response of the infant to the CMV infection.

Although hepatosplenomegaly is common in congenitally CMV-infected infants, chronic hepatitis and its resultant sequelae are rare.[15,23-25] Typically, the biochemical and histologic evidence of CMV-associated hepatic injury resolves within a couple of months. One child had residual mild hepatic fibrosis on biopsy of a liver specimen at age 4 years.[26] A recent article described a symptomatic, congenitally infected infant who died at age 3 months of end-stage liver disease secondary to diffuse hepatic fibrosis.[27] In this case, the biliary epithelium was not affected by the infection.

Although relatively rare, severe liver disease has been reported following CMV infection. Oppenheimer and Esterly[18] described an infant with cystic fibrosis and congenital CMV infection who also had cholestasis and paucity of bile ducts. Hepatic lesions in CMV-infected infants include hepatic fibrosis, hepatic necrosis, giant-cell transformation, cholestasis, extrahepatic hematopoiesis, and large intranuclear inclusions.[17,27] Previous reports have documented concomitant CMV infection and biliary atresia,[17-19] but a convincing cause-effect relationship has yet to be documented. Finegold and Carpenter[28] described a fetus at 24 weeks' gestation with obliterative intrahepatic cholangitis associated with CMV infection, and proposed that similar in utero CMV infection might play a role in the development of some cases of EHBA. Undoubtedly, host factors affect the expression of CMV infection in the developing fetus and newborn infant. This could certainly account for the discordant presence of liver disease in the infants in our study, despite similar exposure to CMV.

Compared with CMV infection in adults, congenital infection results in more variable findings. Typically, it causes more extensive hepatocellular injury. Widespread multinucleated giant cells with or without bile duct proliferation, areas of fatty metamorphosis, cholangitis, interstitial fibrosis, and periportal fibrosis are frequently seen.[17,25,29] Intranuclear and cytoplasmic inclusions are often seen in the hepatocytes, with endothelial cells, and in bile duct epithelium. Functional obstruction of bile ducts is not uncommon, and is presumably mediated by mechanical obstruction of the canalicular lumen by edematous CMV-infected cells.[30-33] Using electron microscopy of tissues from a congenitally infected infant, Balazs[34] found viral particles or inclusions in bile duct cells (both at nuclear and cytoplasmic locations) and intraluminally in the bile duct and the duodenum.

Our infants exhibited evidence of prenatally acquired CMV infection, with an evolving pattern of postnatal development of EHBA (twin B) and of neonatal hepatitis (twin A). The postnatal development of signs of progressive hepatocellular injury with cholestasis in twin B was temporally associated with CMV infection, as documented by a positive immunoperoxidase stain, a positive cDNA probe, and a viral culture of liver specimens that yielded CMV. Subsequent cultures of liver specimens on day 35 did not yield CMV. The occurrence of EHBA coincident with primary CMV infection suggests a causative role of CMV in the evolution of hepatocellular injury and the development of EHBA. It should be clarified that this does not confirm the role of CMV in EHBA.

Although CMV infection is a quite common congenitally acquired infection, the development of CMV and EHBA is rare in newborns. Although prenatally acquired CMV infection is associated with EHBA and neonatal hepatitis in the infants in our study, most cases of EHBA and neonatal hepatitis occur without associated viral infections. The discordance in disease expression is probably most accurately attributed to unknown differences in host responses.

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Breast-feeding Initiation in a Triethnic Population

David E. Bee, PhD†; Tom Baranowski, PhD; David K. Rassin, PhD; C. Joan Richardson, MD; William Mikrut, MS

• The influence of sociodemographic factors on the initiation of breast-feeding was evaluated in a triethnic population from Galveston, Tex. Breast-feeding rates were 44.3% among Anglo-Americans, 13.5% among blacks, and 26.6% among Mexican-Americans. Mexican ethnicity, education levels among Anglo-Americans, and marital status were associated with the initiation of breast-feeding. Odds ratios for breast-feeding were 1.94 (95% confidence interval, 1.10 to 3.43) times higher in Mexican-American compared with black women, and 1.94 (95% confidence interval, 1.34 to 2.83) times higher in married than unmarried women. Anglo-American ethnicity and education, as main effects, were not significantly associated with breast-feeding, but their interaction was. Among Anglo-American women (in comparison with black women), the odds ratios of breast-feeding increased with education level, ranging from 1.84 for those with less than an eighth grade education to 7.46 for those with some college. In contrast to recent findings suggesting that education was more important than ethnicity in predicting breast-feeding, the odds of breast-feeding among Anglo-American compared with black women depended on the level of maternal education, but the odds of breast-feeding for Mexican-American vs black women did not depend on education.

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The prevalence of breast-feeding at the time of discharge from the hospital in the United States has declined over the last few years to about 55% in 1988 after reaching a high of about 62% in 1984[1-3] (Gilbert A. Martinez, MBA, Ross Labs, Columbus, Ohio, unpublished report, November 23, 1988). This recent decline represents a reversal of the trend to increased breast-feeding incidence that started in the early 1970s, when only about 25% of babies were breast-fed on discharge from the hospital. The recent decline in breast-feeding incidence has taken place despite efforts by professional groups[4,5] and the Surgeon General of the United States[6] to encourage a greater incidence of breast-feeding. Better understanding of the factors that influence breast-feeding should serve to promote this important health behavior.

A number of demographic factors, such as education, income, age, parity, working status, and ethnicity,[1-3,7,8] have been bivariately associated with breast-feeding. Ethnicity has been consistently highly associated with breast-feeding.[3,7,9,10] For example, in 1985, 64% of white, 51% of Hispanic, and 29% of black mothers in the United States were breast-feeding their infants at discharge from the hospital.[3] These ethnic group differences were magnified within the southern and central regions of the United States.[3] Kurinij and colleagues,[11] however, reported that when using more sophisticated statistical techniques, ie, logistic regression, differences in education were more important than differences in ethnicity as a predictor of breast-feeding. Ethnic group differences suggest that cultural differences across the ethnic groups, eg, in expectancies[12,13] or social support,[14] affect the decision to breast-feed. The fact that education was an important predictor suggests that some aspect of social class characteristics affects the initiation of breast-feeding. As a result, whichever factor is more important will affect the kind of program designed to promote breast-feeding. Since little is known about demographic predictors of breast-feeding using multivariate data analysis techniques, the relative influence of ethnicity and education was reexamined in a large triethnic data set using log-linear and logistic regression techniques.

SUBJECTS AND METHODS

Demographic and initial infant-feeding characteristics of participants from two previous studies (August 1981, August 1983, and January 1984)[9,13] were combined to permit a sufficiently large sample to address the research questions. Both studies were reviewed and approved by the University of Texas Medical Branch (Galveston) Institutional Review Board. Data on maternal ethnicity, age, education, employment status, marital status, income, and gravidity were obtained from 881 completed questionnaires. These questions were worded using a standard format[15] adapted to local use. Breast-feeding initiation as a variable was defined to include breast-feeding in the hospital at the time of the survey. Breast-feeding status was both self-reported and verified with the nursery nurse. In all cases, there was perfect agreement between mother and nurse. Fifty subjects were deleted from the analysis, leaving 831 with complete information for the demographic variables of interest. Twenty-seven of the 50 deleted subjects were classified in another ethnicity group and 23 had at least one missing observation for the variables of interest.

Data analyses were conducted in two stages. First, a log-linear analysis[16] was conducted to determine the nature of potential relationships (ie, potential interactions) among the categorical demographic variables and breast-feeding initiation. The classic χ^2 analysis for a two-dimensional contingency table can be thought of as a test for a two-factor interaction between the rows and columns of the table. That is, a significant observed χ^2 value implies that the pattern of cell frequencies across columns (rows)

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From the Department of Pediatrics, Georgia Prevention Institute, Medical College of Georgia, Augusta (Dr Baranowski); and the Division of Perinatal Pediatrics (Drs Rassin and Richardson) and the Office of Academic Computing and Biostatistics (Mr Mikrut and Dr Bee), The University of Texas Medical Branch, Galveston.

†Deceased.

Reprint requests to Medical College of Georgia, Georgia Prevention Institute, Augusta, GA 30912-3710 (Dr Baranowski).

Table 1.—Frequency Distributions by Demographic Characteristics of All Mothers and Mothers Breast-feeding*

Variables	No. (%) in Study Group	No. (%) Breast-feeding	χ^2 (df), P
Maternal ethnicity			
Anglo-American	402 (46.3)	178 (44.3)	73.5 (3), <.001
Black	266 (30.7)	36 (13.5)	
Mexican-American	173 (19.9)	46 (26.6)	
Other	27 (3.1)	11 (40.7)	
Age (y)			
Adolescent (13-17)	135 (15.6)	33 (24.4)	8.7 (3), .033
Young (18-21)	293 (34.0)	87 (29.7)	
Adult (22-25)	243 (28.2)	75 (30.9)	
Older (26-43)	192 (22.3)	75 (39.1)	
Marital status			
Married	558 (64.2)	215 (38.5)	39.5 (2), <.001
Single	222 (25.6)	38 (17.1)	
Other	89 (10.2)	18 (20.2)	
Employment status			
Unemployed	495 (56.9)	149 (30.1)	0.7 (1), .395
Employed	375 (43.1)	123 (32.8)	
Education			
Grade 8 or less	123 (14.2)	35 (28.5)	29.2 (3), <.001
Some high school	298 (34.3)	76 (25.5)	
Graduate of high school and/or technical school	281 (32.3)	80 (28.5)	
Some college	167 (19.2)	81 (48.5)	
Annual income, $†			
<5000	165 (36.3)	48 (29.1)	12.5 (2), .002
5000 to 15 000	203 (44.6)	77 (37.9)	
>15 000	87 (19.1)	45 (51.7)	
Gravidity			
First	291 (33.6)	101 (34.7)	2.5 (2), .293
Second	245 (28.3)	74 (30.2)	
Third or more	330 (38.1)	96 (39.1)	

*Statistical tests are for equality of breast-feeding proportions.
†Data were not reported for 426 mothers.

is not the same for all rows (columns). The log-linear analysis (while not using the χ^2 test for two categories) extends the notion of testing for interaction to tables of higher dimensions with potentially higher-order interactions. For example, a four-dimensional contingency table (subjects classified by four criteria) could exhibit a statistically significant four-factor interaction, as well as significant three- and two-factor interactions. Higher-order interactions can be difficult to interpret. Different combinations of possible effects are combined into models and tested for goodness of fit. The G^2 statistic provides the goodness of fit of a log-linear model. The G^2 statistic should be nonsignificant for the fit of a model to be considered good. The log-linear analysis permits the estimation of cell effects, which aids in the interpretation of significant higher-order interactions. Interactions are described by *u* terms, which reflect the relative strength of relationships among variables.

For this analysis, education level, defined by years of schooling completed, was dichotomized into low and high groups. Mothers in the high category had at least a high school diploma or equivalent. Age was partitioned into four categories, representing adolescent (13 to 17 years), postadolescent (18 to 21 years), young adult (22 to 25 years), and older (26 to 43 years) mothers. A base model strategy was employed using the CATMOD procedure of SAS[17] to obtain G^2 goodness-of-fit statistics and model parameter estimates. The G^2 statistic has an approximate χ^2 distribution and is equal to 0 if estimated cell frequencies are exactly equal to observed cell frequencies (a perfect fit of the model). The base model consisted of ethnicity, marital status, categorized age, categorized education, and all possible interactions among these four main effects.

Table 2.—Estimated Interaction *u* Terms Corresponding to Estimated Expected Values From Log-Linear Analysis of Breast-feeding, Ethnicity, and Education

		Breast-feeding	
Ethnicity	Education Level	No	Yes
Anglo-American	Low	0.162	−0.162
	High	−0.162	0.162
Black	Low	−0.084	0.084
	High	0.084	−0.084
Mexican-American	Low	0.078	−0.078
	High	−0.078	0.078

The second stage used linear logistic regression to predict initiation of breast-feeding (no, yes). The logistic model included the main effects (specific demographic variables) and interactions suggested by the log-linear analysis. Age was considered at this second stage as a continuous variable, while education was coded as a four-category ordinal response, where 1 is grade 8 or less, 2 is some high school, 3 is graduate of high school and/or technical school, and 4 is at least some college. The base model strategy was also used in the logistic analysis.[18,19] For example, if an interaction term between two explanatory variables had a statistically significant coefficient ($P \leq .05$ as a stepwise entrance criterion), then both explanatory variables were included in the model regardless of their level of significance. Adjusted odds ratios and corresponding confidence limits are based on the estimated parameters of the linear logistic regression model.[18]

RESULTS

Pairwise Associations

Frequency distributions of demographic characteristics and their pairwise relationships with breast-feeding status are given in Table 1. Differences in sample size across characteristics are due to missing information. Statistical significance of the pairwise associations (as assessed by χ^2 analysis) indicates that the initiation of breast-feeding was not independent of maternal ethnicity, marital status, education, or income. The association between age and breast-feeding initiation ($P = .033$), however, is weak and would not be considered statistically significant if an experimentwise error rate of $\alpha = .05$ is to be achieved. That is, with seven tests, each individual inference should be made with an error rate set at $.05/7 = .0071$. The combined data set revealed the same pattern of breast-feeding responses as observed in the two previous studies.[9,13]

Relative to ethnicity, the highest proportion of women breast-feeding was observed for the Anglo-American group (44.3%) compared with a low of 13.5% for blacks. Older women (26 to 43 years) exhibited the highest incidence of breast-feeding (39.1%) among the four age categories, and married women and women with a higher education showed the highest proportion of breast-feeding in their respective categories (38.5% and 48.5%).

Log-Linear Analysis

The initial log-linear analysis revealed that categorized age in the presence of marital status, ethnicity, and education was not significantly related to breast-feeding initiation. Thus, age was dropped from the base model and

Table 3.—Adjusted Odds Ratios for Breast-feeding Initiation ($n = 831$)

Terms in Logistic Regression Model	Odds Ratio	95% Confidence Limits
Anglo-American vs black for		
Grade 8 or less	1.84	0.82, 4.11
Some high school	2.93	1.73, 4.98
Graduate of high school and/or technical school	4.68	3.05, 7.19
Some college	7.46	4.11, 13.57
Mexican-American vs black	1.94	1.10, 3.43
Marital status	1.94	1.34, 2.83

a new analysis was initiated. This search resulted in a model with excellent fit ($G^2 = 2.04$, $df = 5$, $P = .8430$) that contained a significantly nonzero three-factor interaction ($P = .0183$) for breast-feeding, ethnicity, and education. In keeping with the base model approach, each of the three variables and all two-factor interactions among these three variables were also included in the model. Of these, all were significantly nonzero ($P < .0001$), with the exceptions of education ($P = .8004$) and the interaction of breast-feeding and education ($P = .1106$). A two-factor interaction between breast-feeding and marital status was also significantly nonzero ($P = .0003$). The three-factor interaction component is displayed in Table 2. The magnitude and direction of the *u* terms revealed that Anglo-American women who had not graduated from high school were less likely to initiate breast-feeding than their more highly educated Anglo-American counterparts. Mexican-American women followed the same pattern as the Anglo-Americans, but the strength of the association was only about half as great. Black women, however, exhibited an opposite pattern, with higher-educated women less likely to initiate breast-feeding.

Linear Logistic Regression Analysis

Blacks were used as a reference category for coding purposes to estimate odds ratios for ethnicity. Anglo-Americans and Mexican-Americans, marital status, education (coded as a four-level ordinal variable), and two two-factor interactions identified by the log-linear analysis (ethnicity by education, ethnicity by marital status) were analyzed as potential explanatory variables for breast-feeding. Age, as a continuous variable, was incorporated in the logistic model as a main effect as well as in two-factor interaction terms with all other variables. This was done to verify that the categorization of age in the log-linear analysis had not disguised a potential age effect. As in the log-linear analysis, age in the presence of the other main effects showed no ability to predict breast-feeding initiation either as a main effect or in any two-factor interaction with other main effects. Thus, age was deleted from the base model. From a stepwise search procedure, the final model consisted of main effects (Anglo-American, Mexican-American, education, marital status) and one two-factor interaction (Anglo-American by education). The model χ^2 value was 117.7 ($df = 5$, $P < .0001$). Sensitivity and specificity of the model were 42.4% and 87.5%, respectively. The total correct classification rate for the complete original sample was 73.5%. The interaction in the model (Table 3) revealed that the odds ratio for Anglo-American women vs black women was an increasing function of the level of education, while the same was not true for Mexican-Americans. That is, as education increased, the disparity in breast-feeding proportions between Anglo-American and black mothers increased, but the odds of Mexican-American women vs black women initiating breast-feeding did not depend on education.

COMMENT

Rassin et al[9] reported that ethnicity was the variable most closely associated with breast-feeding initiation, with the implication that something about cultural practices or relationships was strongly affecting this important infant feeding practice. Kurinij et al[11] reported that education was more closely associated with breast-feeding initiation than was ethnicity, implying that social class was the primary determining factor. The current reanalysis of combined earlier data sets[9,12] using more sophisticated statistical procedures revealed an interaction between education and ethnicity: education is an important factor, but only among Anglo-American in comparison with black mothers. As education increased, Anglo-American mothers were more likely to breast-feed in comparison with black mothers. Education was independent of breast-feeding initiation for Mexican-American mothers, with Mexican-American mothers being 1.94 times as likely to initiate breast-feeding as black mothers, regardless of education level.

Several reasons could explain the differences between the results of Kurinij et al and the current findings, including regional differences, characteristics of the samples, and methods of analysis. Martinez and Krieger[3] reported regional differences in breast-feeding prevalence. Regional differences in associations among variables are equally comprehensible, if difficult to interpret. What it is about the regions that might induce different associations requires further thought and research.

Sociodemographic characteristics of the current sample indicate a young triethnic group with a low to moderate level of education and high unemployment. Of incomes reported (455 of 881 subjects), only 19.1% were above $15 000 per year. The educational attainment in the current black and Anglo-American samples was equivalent, in contrast to the lower educational attainment of the black population reported on by Kurinij et al.[11] The Mexican-American group generally had a lower education level than the other two groups. Breast-feeding rates, regardless of ethnicity, were lower in the current sample than those reported by Kurinij et al[11] or Martinez and Krieger.[3] Perhaps the predominantly lower social class composition of the present sample accounted for these differences.

Another important difference between the present study and that of Kurinij and coworkers was in the analysis procedure itself. Their technique for determining odds ratios did not include potential interaction terms among the demographic variables. If interactions involving specified risk factors are significant, the adjusted odds ratios must be modified accordingly.

The Anglo-American–by-education interaction revealed that as the education level of mothers increased, the proportion of Anglo-American mothers who breast-fed increased relative to the proportion of black mothers. Since education level is most clearly interpreted as a proxy variable for social class, it is apparent that the norm for breast-feeding significantly differs between the middle class of the two groups. Perhaps middle-class blacks have a greater pressure to return to work (which has been shown to affect breast-feeding patterns[8]), or perhaps the message about the extensive benefits of breast-feeding has not permeated the black middle class. Why Mexican-American mothers were more likely than black mothers to breastfeed is unclear but may be related to acculturation processes.[20] These issues require further, more intensive analysis in future studies.

Specificity for the predictive model was relatively strong (87.5%), while sensitivity was relatively weak (42.4%). Thus, the ability to predict mothers who did not initiate breast-feeding was reasonably good, but the ability to predict mothers who did breast-feed was poor. This indicates that demographic characteristics provide an important first approximation to understanding breast-feeding initiation, but these variables must be supplemented with other, more closely related variables. For example, Baranowski et al[13] have shown that attitudes toward infant-feeding vary by ethnicity, and Baranowski et al[14] have shown that sources of social support vary by ethnicity, both of which may account for some of these ethnic group differences.

A limitation of the current study is that it deals exclusively with the initiation of breast-feeding. Many mothers stop breast-feeding soon after they leave the hospital, which is not taken into account in these analyses. However, if mothers do not initiate breast-feeding, they cannot maintain it, and the factors maintaining breast-feeding may differ from those leading to its initiation.[21] Another limitation is that this study includes a sample of generally lower-income mothers from one Southwestern city. The results may not be generalizable to other samples. Finally, some statisticians prefer that a model developed on one sample be shown to have predictive value in a second independent sample before concluding that an interaction term is significant. Further research must be conducted to validate the current interaction terms.

All prospective mothers should receive messages encouraging breast-feeding to promote the health and well-being of their infants. If the findings of the current study are verified at other sites, a stronger message must be addressed to black mothers in general, and middle-class black mothers in particular. The content of this message, or other approaches to intervention, should emerge as further research delineates the roles of cultural factors in these ethnic groups.

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Esophageal Motility in Children With Hirschsprung's Disease

Annamaria Staiano, MD; Enrico Corazziari, MD; Maria Rosaria Andreotti, MD; Ray E. Clouse, MD

• **Esophageal motility was studied in 12 children with Hirschsprung's disease to see if extracolonic motor dysfunction was present in this disorder. Manometric tracings were compared with those from eight children with idiopathic megacolon and from 10 children without esophageal disease or constipation. Amplitude of esophageal contraction waves was significantly higher in children with Hirschsprung's disease than in the other two groups. Swallows that were followed by simultaneous contractions or double-peaked waves were also more common in the group with Hirschsprung's disease (subjects with Hirschsprung's disease, subjects with megacolon, and controls: 57%, 10%, and 8%, respectively). Lower esophageal sphincter characteristics did not differ among the three groups. The increase in simultaneous contractions and double-peaked waves persisted in those children who were reexamined following surgery for Hirschsprung's disease, whereas wave amplitudes fell to a level similar to that observed in the other groups. These data suggest that gastrointestinal motor dysfunction in persons with Hirschsprung's disease is not restricted to the colon, and that some of the observed abnormalities in esophageal motility do not reflect nonspecific responses to megacolon or colonic obstruction.**

(*AJDC*. 1991;145:310-313)

It is well recognized that Hirschsprung's disease may directly or indirectly affect neuromuscular function throughout the colon, but little attention has been given to gastrointestinal motility proximal to this organ.[1] Although any observed abnormalities in extracolonic motor dysfunction could be secondary to megacolon or colonic obstruction, it is clinically recognized that children with this disease often have more severe gastrointestinal distress (including anorexia and failure to thrive) than other children with megacolon and constipation.[1,2] The aim of our investigation was to study esophageal motility in children with Hirschsprung's disease in the preoperative and postoperative setting and compare the findings with those of studies from subject groups with idiopathic megacolon or with no esophageal or colonic complaints.

SUBJECTS AND METHODS

The study population consisted of 12 children with Hirschsprung's disease (11 boys; mean±SEM age, 2.4±0.5 years [age range, 0.5 to 5 years]) and two control groups, ie, eight children with idiopathic megacolon (seven boys; mean±SEM age, 7.4±1.6 years [age range, 3 to 13 years]) and 10 children without esophageal or bowel complaints matched for age to the children with Hirschsprung's disease (six boys; mean±SEM age, 2.0±0.5 years [age range, 0.5 to 5 years]). All subjects were recruited from Naples, Italy. Further clinical characterization of the two subject groups with colonic disease is described in Table 1.

Hirschsprung's disease and idiopathic megacolon were diagnosed by findings from a barium enema, anorectal manometry, and suction biopsy (Noblett capsule), or deep rectal biopsy. In eight of 12 children with Hirschsprung's disease, a barium enema revealed a narrowed segment that was limited to the rectum and rectosigmoid. In one other subject, this segment extended to the transverse colon, and in the remaining three subjects, colonic dilatation extended to the anus without an apparent narrowed segment. In each subject with Hirschsprung's disease, the rectal inhibitory reflex was absent by anorectal manometry, and ganglion cells were not found on rectal biopsy specimens. All children with Hirschsprung's disease underwent surgery, and six were available for repeated manometric examination 3 months after the operation when symptoms had disappeared or had significantly improved.

Children with idiopathic megacolon had abnormal stool frequency (<4/wk) for more than 1 year in all cases. In three of eight children, the onset of constipation occurred in the first year of life; in the remaining five subjects, the onset of symptoms was between 2 and 4 years of age. Dilatation of the rectum and sigmoid was present on barium enema examination in all eight children. A normal rectoanal response (consisting of three successive pressure falls immediately following rectal distention and a transient pressure fall during prolonged rectal distention), as well as normal ganglion cells on superficial rectal biopsy specimens, were required for this diagnosis.

Ten additional control subjects were children who were being investigated for symptoms that originally suggested gastroesophageal reflux. None of these subjects were ultimately found to have any esophageal (including esophagitis) or colonic disorders. Final diagnoses in this group were as follows: overfeeding vomiting (two children), upper respiratory tract infection (four children), and urinary tract infection (four children).

Esophageal Manometry

Manometry was performed in fasting children without sedation according to a previously described method.[3] In brief, sub-

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From the Department of Pediatrics, II School of Medicine, University of Naples (Italy) (Drs Staiano and Andreotti), the Division of Gastroenterology I, Second Medical Clinic, La Sapienza University, Rome, Italy (Dr Corazziari), and the Division of Gastroenterology, Washington University School of Medicine, St Louis, Mo (Dr Clouse).

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Reprint requests to Dipartimento di Pediatria, II Facolta' di Medicina e Chirurgia, Via S Pansini, 5, 800131 Naples, Italy (Dr Staiano).

Table 1.—Clinical Features in Children With Hirschsprung's Disease and With Idiopathic Megacolon

Sign or Symptom*	No. (%) of Children Hirschsprung's Disease (n=12)	Idiopathic Megacolon (n=8)
Constipation	12 (100)	8 (100)
Delayed passage of meconium	3 (25)	0 (0)
Recurrent fecal impaction	12 (100)	3 (38)
Vomiting	6 (50)	1 (12)
Failure to thrive	5 (42)	1 (12)
Abdominal distention	12 (100)	4 (50)
Palpable stool in rectal ampulla	3 (25)	8 (100)

*As defined according to Tunnessen.[19]

Table 2.—Manometric Features of the LES in the Three Subject Groups*

Subject Group	Mean±SEM Basal LES Pressure, mm Hg	LES Relaxation, % of Basal LES Pressure
Hirschsprung's disease (unoperated)	24.1±1.5	99±1
Idiopathic megacolon	23.2±1.9	98±1
Control children	24.4±2.1	99±1

*LES indicates lower esophageal sphincter.

jects in a supine position were studied with the use of a triple-lumen polyvinyl catheter (outside diameter, 2.4 mm) with radially oriented side openings that were spaced at 2.5 cm. The lumina were perfused with a low-compliance pneumohydraulic system at a rate of 0.5 mL/min. The recording probe was initially placed so that all side openings were in the stomach, and then, it was withdrawn at 0.5-cm intervals through the esophagus. Lower esophageal sphincter (LES) pressure was measured as the maximal midrespiratory pressure by using mean intragastric pressure as the zero reference (slow pull-through technique). The mean of the three luminal determinations was reported. Manometry of the esophageal body was performed with the distal side hole placed immediately above the LES. To assess peristaltic activity, only waves that were induced by wet swallows (1 to 2 mL of 5% dextrose), preceded by 30 seconds or more of absent motor activity, were used. Contraction wave parameters (amplitude and duration) were only measured from the distal esophagus. All constipated children underwent esophageal manometry during continuous treatment with daily enemas to avoid fecal impaction. Medications were withheld for at least 24 hours before manometry in all subjects.

Tracings were coded and analyzed in our conventional way[3] by one of the authors (M.R.A.) who was unaware of the clinical status of the child. The following esophageal motility parameters were recorded: basal LES pressure, LES relaxation with swallowing (as a percentage), distal contraction wave amplitude, distal contraction wave duration, and number of abnormal motor responses (as a percentage of assessable swallows). Abnormal motor responses consisted of simultaneous contraction sequences (velocity, >6.25 cm/s) and double-peaked waves.[4] Manometric measurements were taken from 10 wet swallows in each subject. In all cases, informed written consent for participation in this study was obtained from the parents, and this investigation was approved by the Ethical Board of the University of Naples (Italy).

Statistical Methods

Data are reported as mean±SEM throughout. Mean values across patient groups were compared by using a one-way analysis of variance. If the one-way analysis of variance revealed significant differences, an unpaired, two-tailed Student's t test was applied for individual comparisons. In all cases, a P value of less than .05 was required for statistical significance. A paired t test was used for presurgery and postsurgery data comparisons.

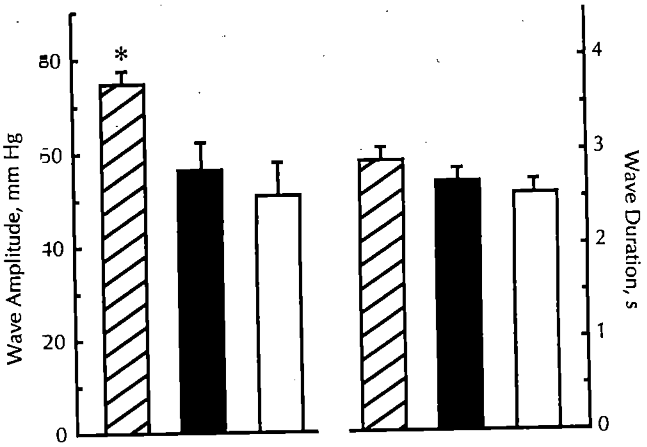

Fig 1.—*Contraction wave amplitudes and durations in the three subject groups. A significant elevation in wave amplitude was noted for children with Hirschsprung's disease prior to operation (hatched bars) when compared with the other two subject groups. (One-way analysis of variance for all groups: wave amplitude,* $P<.01$*; wave duration,* $P=.03$*.) Asterisk indicates* $P<.05$ *compared with each of the other two groups; solid bars, subjects with idiopathic megacolon; and open bars, control children.*

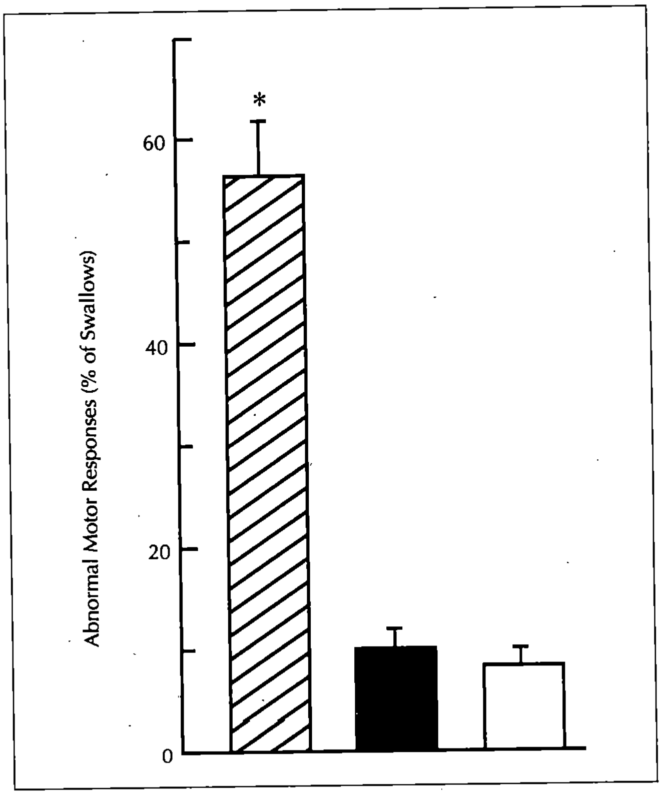

Fig 2.—*Frequency of abnormal motor responses (simultaneous sequences and double-peaked contraction waves) following swallows for each subject group. Abnormal motor responses were more commonly seen in children with Hirschsprung's disease prior to operation (hatched bar) than in each of the other two subject groups. (One-way analysis of variance for all groups* $P<.001$*.) Asterisk indicates* $P<.001$ *when compared with each of the other two groups; solid bar, subjects with idiopathic megacolon; and open bar, control children.*

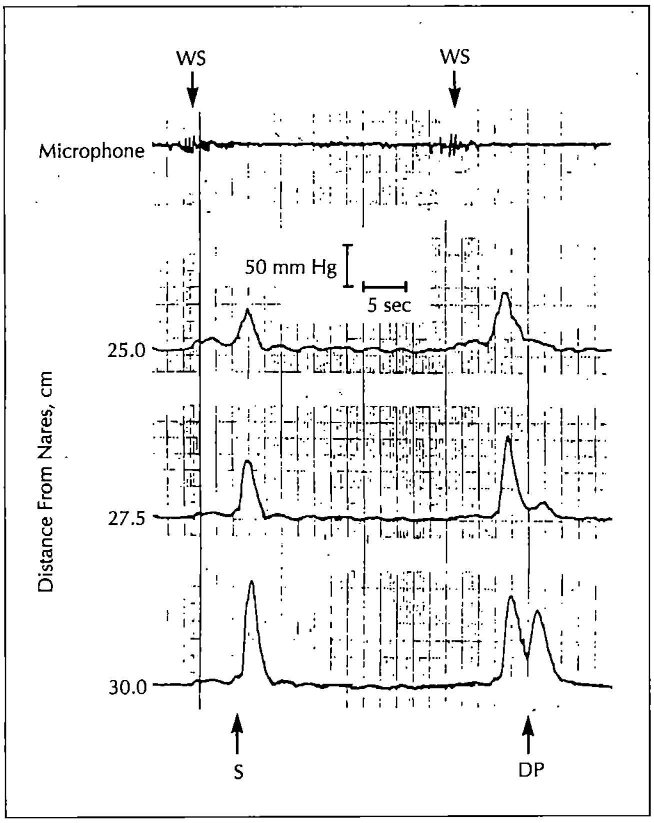

Fig 3.—*A manometric tracing from one of the subjects with Hirschsprung's disease shows a simultaneous contraction sequence (S) following one wet swallow (WS) and a double-peaked response (DP) on the subsequent swallow. All three recording ports were in the distal esophagus.*

RESULTS

No significant intergroup differences were detected in the manometric characteristics of the LES (Table 2). Distal contraction wave amplitudes were, however, significantly elevated in the children with Hirschsprung's disease when compared with those amplitudes in the other two groups (Fig 1). No differences in distal wave duration were detected. Analysis of the manometric tracings for abnormal motor responses (simultaneous contraction sequences and double-peaked waves) revealed differences among the groups (Fig 2). An example of a manometric tracing that shows both a simultaneous sequence and a double-peaked response is provided in Fig 3. A significantly greater percentage of swallows were followed by abnormal motor responses in the children with Hirschsprung's disease when compared with the responses in the other two groups ($P<.001$ for each comparison). As with wave amplitude and duration, the subjects with idiopathic megacolon did not differ from the control group.

Manometric results before and after operative treatment of Hirschsprung's disease are shown for six subjects in Fig 4. The Soave procedure was performed in three children, the Duhamel procedure was performed in two, and anorectal myectomy was performed in one. Findings in the control children are included in Fig 4 for comparison. Contraction wave amplitude significantly decreased in the postoperative period ($P<.05$), such that differences between subjects with Hirschsprung's disease and the control children were no longer evident (Fig 4). However, the increased frequency of abnormal motor responses was not influenced by operative correction of Hirschsprung's disease (Fig 4, bottom).

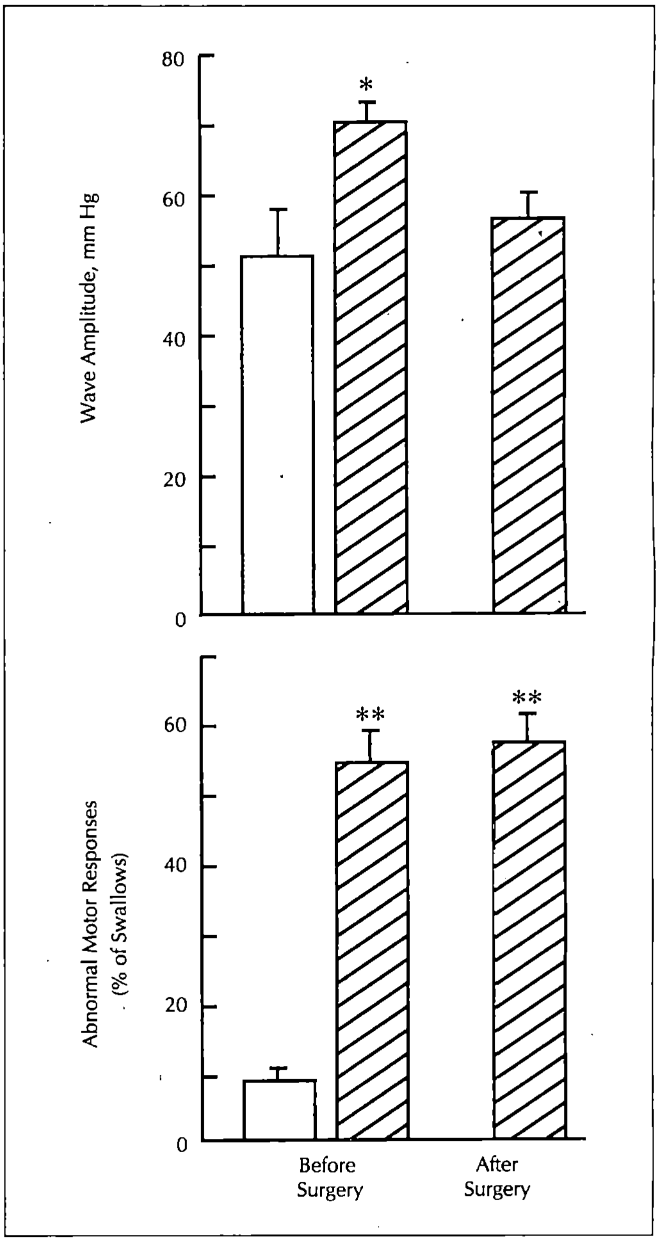

Fig 4.—*Manometric findings in six children before and 3 months after operative treatment of Hirschsprung's disease (hatched bars). Findings in the control children (open bars) are included on the figure for comparison. One asterisk indicates* $P<.05$; *double asterisks,* $P<.001$ *when compared with control children.*

COMMENT

These data demonstrate that motor abnormalities are detected in the esophagi of children with Hirschsprung's disease who have not yet undergone operations; some of these abnormalities do not resolve with surgical treatment of the colonic disorder. Previous reports of this disease have focused only on neuromuscular dysfunction of the colon. However, it would appear that more diffuse gastrointestinal motor dysfunction may be subclinically present. Esophageal motor abnormalities were not related to the extent of colonic aganglionosis in our subjects, and previous studies have suggested an inconsistent correlation between the degree of colonic involvement and the clinical course.[5,6]

The high prevalence of abnormal motor responses to swallows, findings that may relate to esophageal neural dysfunction,[7] were not nonspecific findings related to colonic disease or to an obstructed state. These abnormalities were not found in the children with idiopathic megacolon and persisted following surgical correction of Hirschsprung's disease. In contrast, the wave amplitudes normalized following surgical correction, making the finding of elevated amplitudes in untreated children of lesser significance. A neuropathologic explanation for these findings is not apparent. To our knowledge, esophageal neural abnormalities have not been described in subjects with Hirschsprung's disease, and results of detailed microscopic examination of the esophagus have not been included in reports of this disease. Contiguous involvement to the stomach has been found in a case of total intestinal aganglionosis,[8] but extreme cases of aganglionosis differ from cases of typical Hirschsprung's disease. At present, Hirschsprung's disease is considered a neurogenic developmental disorder with a heterogeneous origin and some heterogeneity in neuropathologic characteristics.[9,10] Chromosomal and genic defects (as well as other undefined factors) are invoked in producing aganglionosis and subsequent functional errors in excitatory and inhibitory neural transmission.[9,11] Whether these basic defects also produce less severe abnormalities in extracolonic myenteric nervous function remains unknown.

We could not show that esophageal motility in children with idiopathic megacolon differed from findings in children without esophageal or colonic disease. Previous studies in some adult subjects with severe idiopathic constipation with and without megacolon have demonstrated diffuse gastrointestinal motor dysfunction with esophageal involvement in many cases.[12-14] An identifiable pathologic condition in extracolonic bowel segments has been found in the neuromuscular apparatus of some of these adult subjects.[14] Although motor dysfunction has been well demonstrated in the distal colon of some children with idiopathic forms of constipation,[15,16] extracolonic motor abnormalities have not been reported and were not found in the present study. The adult and childhood varieties of severe idiopathic constipation differ also in other regards: in the former, symptom onset is rarely in the first decade of life, females predominate, and the conditions of many adults improve only after colectomy.[13] In the latter, onset is in early childhood, males predominate, and surgery is rarely needed.[17]

Distinct esophageal complaints are not recognized as a component of Hirschsprung's disease.[18] However, it is clinically acknowledged that children with this disorder frequently have more gastrointestinal complaints (including anorexia and failure to thrive) than other subjects with megacolon.[1,2] The present data suggest that neuromuscular dysfunction in this disease may be more diffuse within the gastrointestinal tract than previously had been appreciated, and further systematic studies of extracolonic motility appear to be merited. Besides potential clinical importance, this concept is relevant when considering the pathogenesis of Hirschsprung's disease.

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Cortical Resection for Children With Epilepsy

Perspectives in Pediatrics

Elaine Wyllie, MD

The potential of cortical resection for epilepsy was first demonstrated by Penfield and Jasper[1] at the Montreal Neurologic Institute (Montreal, Quebec) in the 1940s and 1950s. The application of this technique in children was emphasized in the 1960s and 1970s[2-8]; since then, it has become apparent that early surgery in selected cases may enable children to become seizure free for a normal transition into adulthood. This may prevent some of the difficult psychosocial problems that occur in adults with longstanding epilepsy, including dependency, poor self-esteem, and long-term vocational disability.[9] In addition, if epilepsy surgery enables a child to discontinue antiepileptic medication, years of exposure to these drugs can be avoided. As pediatricians become better acquainted with surgical options, patients are benefiting from earlier referral for surgery. The purpose of this review is to inform children's physicians about the indications for referral and new approaches to surgical management of pediatric epilepsy.

For editorial comment see p 256.

TEMPORAL LOBECTOMY

Selection of Candidates

Clinical Features.—Temporal lobectomy can successfully control seizures in children and adults with temporal lobe epilepsy. Patients typically have complex partial seizures,[10] with or without secondarily generalized tonoclonic convulsions, and the electroencephalogram (EEG) shows focal epileptiform discharges from the temporal lobe (Fig 1).

The seizures of temporal lobe epilepsy typically begin in middle childhood or adolescence but may occur earlier. Epilepsy surgery series note onset of seizures in children as young as 2 or 3 years old; in one study of pediatric patients with temporal lobe epilepsy, 16% had onset of seizures before age 2 years.[11] However, the duration from onset of seizures until epilepsy surgery is often many years. In one series, the average delay until operation was 13.6 years from onset of seizures and 11.3 years from onset of medical intractability.[12] This delay is often due to delayed referral to special centers.

Complex partial seizures in children older than 6 or 7 years often involve clinical features similar to those seen in adulthood. They may begin with an unusual sensation (aura) preceding loss of consciousness or may proceed directly to alteration of awareness, unresponsiveness, and repetitive semipurposeful automatic movements.[13-16] The automatisms may be oral, gestural, or ambulatory and are often stereotyped for individual patients from one seizure to another. Seizures may also involve emotional expressions, such as anger, laughing, or fear; afterward, the child may seem agitated and upset due to postictal confusion. Patients have at least partial amnesia for ictal events. Some have secondarily generalized tonic-clonic convulsions, but others with temporal lobe epilepsy have only complex partial seizures for many years.

In infants and young children, the clinical manifestations of complex partial seizures may be subtle, making the diagnosis more difficult.[11,13,14] If an aura occurs, it may not be appreciable in the nonverbal child unless he or she is able to run to the parents for help at the onset of an attack. Staring, altered awareness, and oral automatisms may be difficult to distinguish from background behavior, especially in infants; the more complex gestural and ambulatory automatisms that are prominent in adulthood are typically absent in younger patients.[17,18] Few studies have addressed the clinical symptoms of complex partial seizures in infants based on video-EEG recording,[17,18] and further research in this area will be important.

Noninvasive EEG Findings.—The EEG hallmark of temporal lobe epilepsy is epileptiform discharges from the temporal lobe (Figs 1 and 2). However, this finding may be less common in young children than in adults, and routine EEGs may be normal.[15,18,19] Definitive diagnosis may require intensive video-EEG monitoring during an attack. An EEG seizure pattern arising from the temporal lobe during a complex partial seizure can confirm the diagnosis (Fig 3).

Origin.—Temporal lobe epilepsy may be due to a slow-growing neoplasm, vascular malformation, trauma, infarction, or previous infection. The epilepsy may also be caused by developmental disturbances, such as cortical dysplasia, with abnormal migration and maturation of neurons during early brain development or by mesial-temporal sclerosis with damage to hippocampal neurons, sometimes secondary to an early hypoxic or ischemic insult. Because of the high incidence of structural lesions, especially in children,[11,20] neuroimaging is important. Magnetic resonance imaging is the test of choice because

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From the Pediatric Epilepsy Program, The Cleveland (Ohio) Clinic Foundation.

Reprint requests to the Pediatric Epilepsy Program, The Cleveland Clinic Foundation, One Clinic Center, 9500 Euclid Ave, Cleveland, OH 44195-5221 (Dr Wyllie).

Department Editor.—*Alan D. Bedrick, MD, Tucson, Ariz*

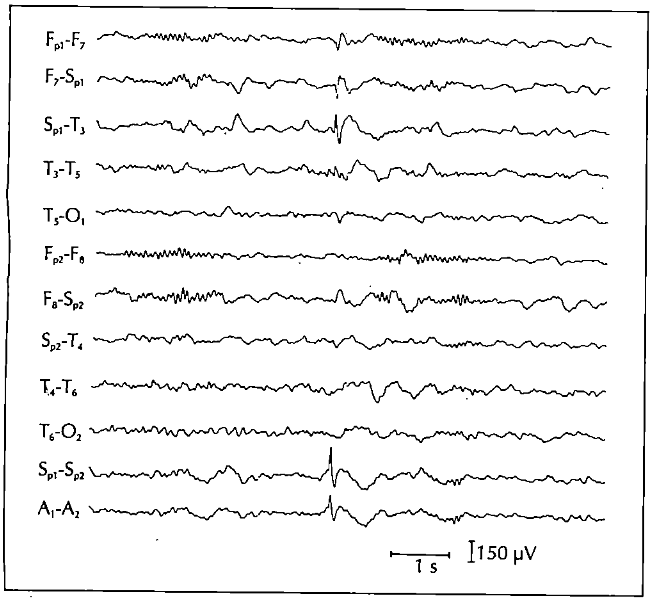

Fig 1.—*Electroencephalogram with an interictal sharp wave in the center of the tracing. The discharge was from the left anterior temporal region, maximal at the sphenoidal (S_{p1}) electrode. This 13-year-old boy had complex partial seizures arising from that area since the age of 7 years and a large low-grade astrocytoma in the same region.*

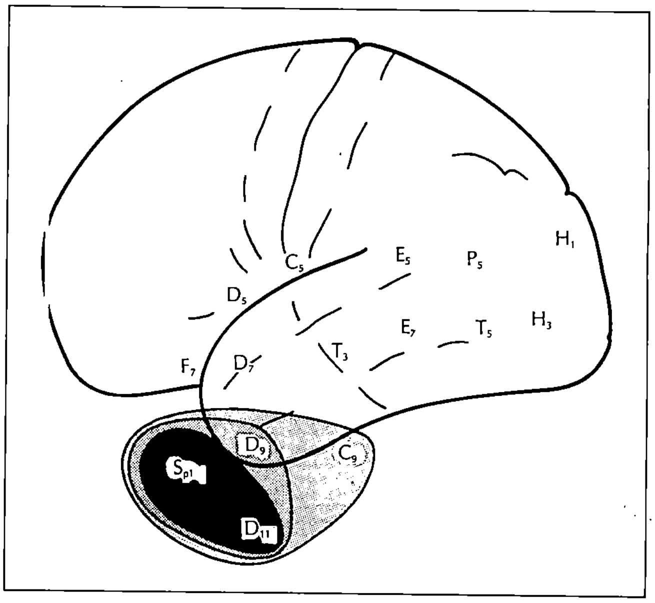

Fig 2.—*Distribution of the electrical field of the epileptiform discharges shown in Fig 1, mapped with the use of special closely spaced surface electrodes. The isoelectric lines indicate the relative voltage of the discharge at each of the electrodes. The amplitude was highest at S_{p1}, 80% as high at D_{11}, 70% as high at D_9, and 60% as high at C_9.*

of its increased sensitivity compared with computed tomography. The presence of a structural lesion on a preoperative magnetic resonance imaging scan may help to direct treatment plans for epilepsy surgery, if the location is concordant with findings seen on the EEG. Additional localizing information may sometimes be gained from positron emission tomography.[21] In cases in which neuroimaging findings are not concordant with EEG localization, the decision to operate is difficult and should be handled on a case-by-case basis.

Intractability, Disability, and Duration.—Issues in the selection of children for epilepsy surgery include medical intractability, degree of disability due to seizures, and lack of realistic hopes for spontaneous remission.

Confirmation of medical intractability requires thorough trials of all major antiepileptic medications, first singly and then in two-drug combinations, to the point of clinical toxicity. The medications most likely to be effective for complex partial seizures include carbamazepine, phenytoin sodium, primidone or phenobarbital, and valproic acid or diralproex sodium. Systematic exploration of these drug regimens is important to rule out the possibility that surgery may not be necessary. The observation time necessary to demonstrate intractability may vary among patients, depending on the baseline seizure frequency. However, most investigators believe that each drug should be used at maximum tolerated dosages for at least 1 month without success, preferably longer, before it is abandoned. Therefore, it usually takes several months to demonstrate medical intractability before epilepsy surgery.

If seizures persist despite maximum tolerated doses of the major medications, further consideration for epilepsy surgery should include careful assessment of the degree of disability caused by the seizures. This may not be solely dependent on absolute seizure frequency or on the presence or absence of secondarily generalized tonic-clonic convulsions. For example, a 6-year-old child with one complex partial seizure a month may be able to have a relatively normal life-style despite the attacks, but the same problem in an older child or adolescent may be severely disabling because of complications for peer relations, driving, dating, sports, employment, and college. On the other hand, one complex partial seizure per week might not add significantly to the disability of a mentally retarded adolescent if seizures do not interfere with lifestyle and employment in a sheltered setting, whereas the same patient's quality of life might be adversely affected by the same frequency of secondarily generalized tonic-clonic convulsions.

The decision whether to proceed to surgery, therefore, must be weighed in the context of the degree of disability due to seizures for each child. However, it should be recognized that for all children, recurrent, unpredictable attacks of altered consciousness may have damaging effects on self-esteem, confidence, and independence. Persistent psychosocial problems are not uncommon in children with uncontrolled complex partial seizures, complicated by parental overprotection and decreased expectations of teachers.[9] These problems may be alleviated by good seizure control after surgery.

Another serious consideration is the chance for spontaneous remission of seizures in children with temporal lobe epilepsy. Adults may present with an intractable seizure disorder that has not changed clinically in 10 or 15 years, and in this setting the likelihood of spontaneous remission is remote. With children, the period of observation is typically shorter, and population data about natural history are more sparse. Previous studies have suggested that childhood-onset epilepsy is more likely than adult-onset epilepsy to remit.[14,22-29] However, these series often did not rigorously exclude patients with benign partial epilepsy of childhood, generalized absence epilepsy, or psychogenic seizures. Only recently have data been collected specifically about children with EEG-documented temporal lobe epilepsy; in these series, the rate of spontaneous remission was low, in the range of 10% to 18%.[11,30]

For selected patients with temporal lobe epilepsy, surgery should be considered before late adolescence.[14,31] If

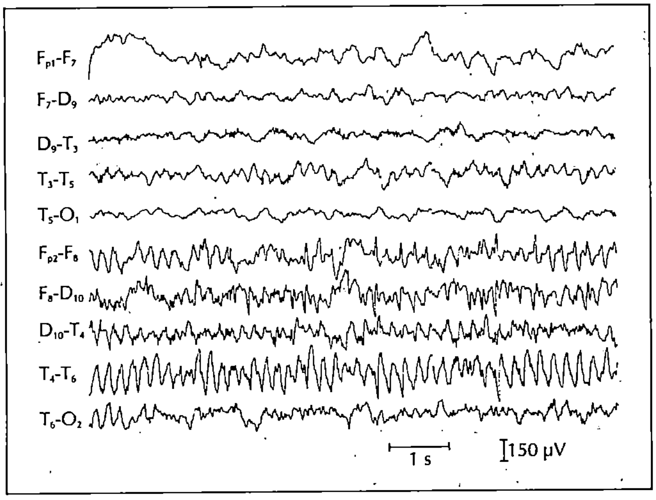

Fig 3.—*Electroencephalogram obtained during a complex partial seizure showing paroxysmal rhythmic epileptiform activity (five per second) from the right temporal lobe (second five channels of recording). This 2-year-old boy had no abnormal epileptiform discharges between seizures, so this recorded seizure pattern was the first electrographic evidence of his epilepsy.*

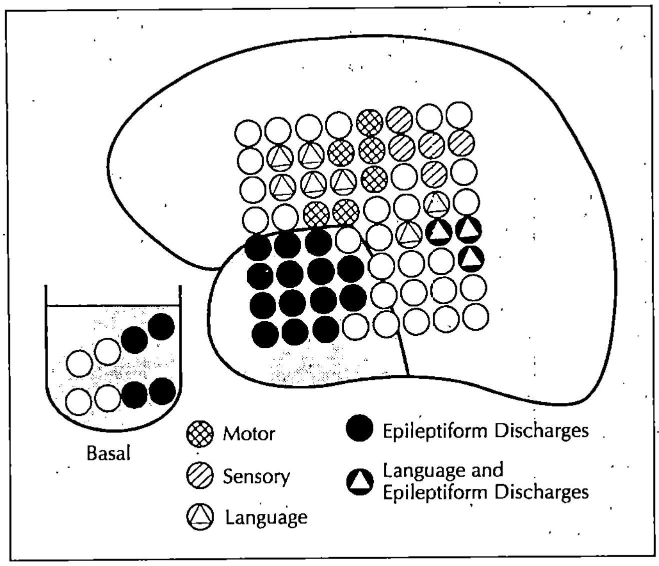

Fig 4.—*Results of subdural electroencephalography and functional localization studies in a 13-year-old boy with complex partial seizures. Invasive studies were performed because surface electroencephalography showed epileptiform discharges from anterior and posterior left temporal regions. With subdural studies, most of the ictal and interictal epileptiform discharges were in anterior and basal temporal regions, but a small percentage were from the region of Wernicke's language area. The anterior epileptogenic focus was resected, but the posterior focus was left behind. There were no operative complications. Six years after surgery, the patient has had only one complex partial seizure and is living independently at college.*

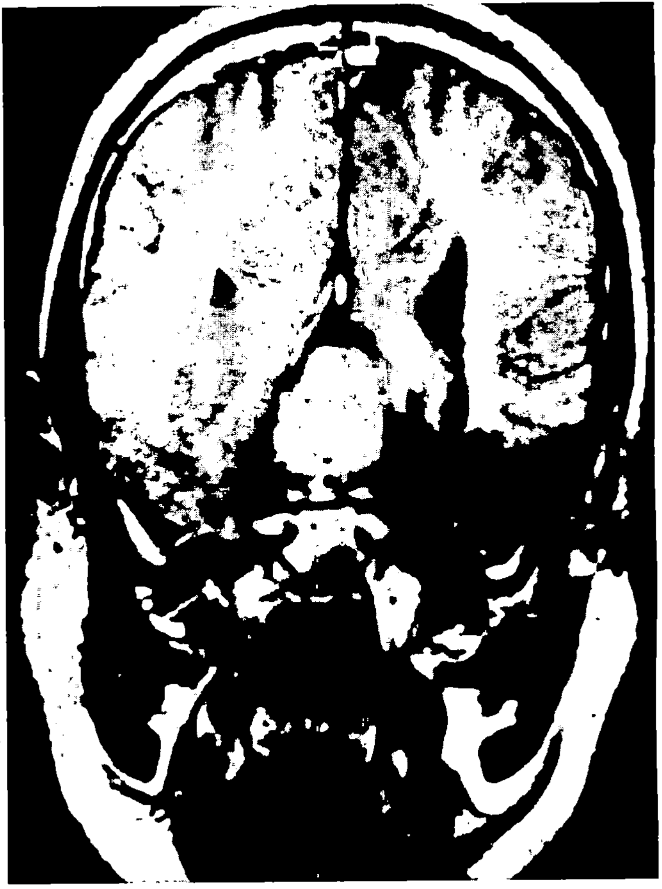

Fig 5.—*T_1-weighted magnetic resonance image after right temporal lobectomy, including resection of the amygdala and hippocampus. This 18-year-old male adolescent had intractable daily complex partial seizures starting in infancy. Since surgery, he has been seizure free for 2 years.*

other selection criteria are satisfied, then earlier surgery may be appropriate. Because temporal lobe epilepsy tends not to manifest as an intractable, disabling problem until at least age 7 or 8 years, it is uncommon for children to present for consideration of epilepsy surgery before that age. This is in contrast to extratemporal epilepsy, which may present as a devastating problem as early as infancy because of many seizures every day.[32]

When referring a child for possible epilepsy surgery, it is important to select an institution with experience in this specialized field. Epilepsy surgery in children requires a team of pediatric neurologists, neuropsychologists, electroencephalographers, and neurosurgeons, as well as a large number of support and technical personnel. These resources are usually centralized at specialized medical centers.

Presurgical Neurophysiologic Evaluation

Careful video-EEG evaluation with scalp electrodes is the cornerstone of planning for epilepsy surgery; special additional scalp electrodes may be added over the area of interest. For patients with possible temporal lobe epilepsy, sphenoidal electrodes may also be helpful (Figs 1 and 2).[33] Sphenoidal electrodes are thin wires that are inserted inside a lumbar puncture needle into the muscles of the face, between the zygomatic process and the angle of the mandible. The lumbar puncture needle is withdrawn, and the electrode wires may remain in place near the region of the foramen ovale, recording epileptiform discharges from the basal temporal region. The sphenoidal electrodes may remain in place for several days or weeks, with minimal discomfort or risk. Placement of sphenoidal electrodes is painful, so sedation in children may be helpful during the procedure.[34]

Video EEG recording of clinical seizures is a critical part of the presurgical evaluation. One technique involves a split video screen displaying the real-time EEG along with the clinical seizure, and another technique involves display of a computer-generated time code on the video screen and the EEG paper printout. Both of these techniques permit precise correlation of ictal clinical and EEG events to enable better understanding of the location of seizure onset. Results are correlated with findings from neuropsychological testing, MRI, and PET to give a complete picture of the epileptogenic tone.

When surface and sphenoidal EEG clearly indicates onset of seizures from the anterior mesial or basal region of one temporal lobe, it may be appropriate to proceed to surgery without invasive study.[12,35] However, if findings are more complex, then further investigation may be necessary.

One such situation is the identification of the origin of seizure onset in the middle or posterior portion of the temporal lobe in the language-dominant hemisphere. The side that is dominant for language and memory function can be determined by the intracarotid amobarbital procedure, in which each cerebral hemisphere is separately anesthetized while the functioning hemisphere is tested for language and memory function. When seizures begin in the middle or posterior portion of the temporal lobe on the dominant side, invasive EEG and electrical stimulation studies may be helpful to map Wernicke's language area in relation to the epileptogenic zone, so that language function can be protected during resection (Fig 4). Cortical stimulation studies can be performed in the operating room after craniotomy with the patient under local anesthesia, but this may be arduous for younger patients.[36,37] Cortical EEG and functional localization studies can be performed outside the operating room, with implanted epidural[38] or subdural[20,39] electrodes. With this technique, arrays of electrodes embedded in sheets of Silastic are placed directly over the dura mater or surface of the brain. Language, motor, and sensory regions can be mapped by passing a small electric current into single subdural or epidural electrodes, with careful observation for signs and symptoms, such as transient interference with language function or tingling or involuntary movement of a part of the body.

Possible complications of subdural electrodes include wound infection or increased intracranial pressure. Wound infection is especially troublesome, with symptoms ranging from transient incision drainage to osteomyelitis. For this reason, subdural electrode grids are only used when detailed neurophysiologic information is necessary for a safe and effective resection. Smaller subdural electrode strips, inserted through burr holes, may have a lower incidence of infection than larger grids placed after craniotomy.

Cortical mapping techniques may be highly successful in older children, adolescents, and adults. However, these techniques may be difficult in young children with limited language abilities and attention span. Under age 5 or 6 years, it may be difficult to map language or sensory regions; rolandic motor regions can still be localized by cortical stimulation or evoked potential responses to median or posterior tibial nerve stimulation.[32] In addition, children under age 2 or 3 years may not show motor responses with the cortical stimulation techniques used in adults for reasons that are unclear.[32,38] Therefore, with current techniques, cortical localization findings in infants may be limited to results of evoked potential studies.[32] New stimulation techniques are needed to achieve better localization of functional areas in the youngest patients.

Other techniques available to selected epilepsy surgery candidates include flexible epidural peg electrodes,[40] foramen ovale electrodes,[41,42] and depth electrodes.[43-45] Each may be helpful in certain circumstances when the area for resection is unclear. Depth electrodes are the most commonly used of these invasive techniques.

Depth electrodes are especially useful when the question is which temporal lobe to resect or whether to resect the frontal or temporal lobe on one side, in the setting of epileptiform discharges from both areas. These needle electrodes are placed stereotactically, with the patient under general anesthesia, through small burr holes. The electrode contacts are implanted directly into the brain and may help to determine which area is generating the majority of seizures. Infrequent complications of depth electrodes include intracerebral hematoma or infection.

Operation

The plan for temporal lobectomy is determined individually for each patient based on EEG and neuroimaging results. When EEG suggests that seizures arise from the mesial-basal temporal lobe, this area is targeted for resection (Fig 5). This can be accomplished in several ways: (1) selective amygdalohippocampectomy with use of microsurgical techniques as developed by Wieser and Yasargil[46]; (2) a "keyhole" resection of the amygdala and hippocampus under direct vision after resection of the anterior temporal tip; or (3) a larger "standard" temporal resection of the amygdala and hippocampus plus several centimeters of lateral temporal cortex, more on the side that is nondominant for language. Controlled, prospective series are needed to evaluate the comparative efficacy and adverse effects of these three surgical approaches.

Complications

The most frequent complication of temporal lobectomy is homonymous superior quadrantanopia due to resection of visual fibers in Meyer's loop in the anterior temporal lobe. This complication most commonly occurs when the resection is extensive. In one series, it occurred in 60% of cases overall.[47] However, in the vast majority of cases, the visual field defect is asymptomatic and discovered only with perimetric testing.[47]

Mild dysphasia may occur after left-sided temporal lobectomy, even with resection only of anterior regions of the temporal lobe. In one adult series, mild dysphasia occurred in 17% of patients who underwent left temporal lobectomy.[47] Memory dysfunction may also occur, especially after left-sided temporal lobectomy in adults with high preoperative memory function.[48-50] The exact incidence of postoperative dysphasia and memory dysfunction in children is unknown, but it has been noted that children and adolescents who become seizure free after temporal lobectomy typically experience improved rather than decreased school performance due to dysphasia or memory dysfunction.

Other rare, persistent adverse effects of temporal lobectomy include hemiparesis or other focal neurologic deficits due to infection, infarction, or bleeding.

Outcome

The overall percentage of children and adolescents with excellent outcome after temporal lobectomy, with either no seizures, rare seizures, or auras only, has ranged from 57% to 100%.[6-8,20,36,38,51-54] Among the subgroup in which EEG and neuroimaging had been performed and in which clinical evidence of epileptogenicity was noted only in the anterior portion of one temporal lobe, the frequency of good outcome has reportedly been as high as 91%.[55] The results generally appear to be at least as good in children and adolescents as in adults.[20]

Many patients who undergo temporal lobectomy are eventually able to discontinue medications. It is possible for some patients to achieve a totally normal life-style after surgery. When this major change occurs early in life, before the development of chronic disability, the chances for normal psychosocial maturation are maximized. The ultimate definition of good outcome includes not only seizure control but also normal integration into the social and vocational fabric of society. It appears that for selected patients, the benefits of temporal lobectomy far outweigh the risks.

EXTRATEMPORAL RESECTION

Selection of Candidates

Temporal lobectomy is overall the most common epilepsy surgery procedure. However, among the small subgroup of infants and very young children who undergo epilepsy surgery, extratemporal resections are more common, especially frontal lobectomy.[32] Factors resulting in earlier surgery for infants and children with frontal, parietal, or occipital lobe epilepsy include earlier onset and a higher frequency of daily seizures.[32]

The seizures of extratemporal epilepsy are characterized by various signs and symptoms depending on which cortical regions are affected.[13] They may appear similar to the complex partial seizures of temporal lobe epilepsy or there may be additional signs or symptoms suggesting an extratemporal onset, such as a visual or somatosensory aura or early, prominent focal motor phenomena. Noninvasive EEG may show focal spikes or sharp waves from the affected area or the epileptogenic zone may be identified with MRI or PET. Causative findings may be similar to those in temporal lobe epilepsy. Cortical dysplasia is a common pathologic finding in pediatric patients.[32]

Presurgical Neurophysiologic Evaluation

The techniques of intensive noninvasive and invasive EEG evaluation are similar to those used in the evaluation of temporal lobe epilepsy. Functional localization studies may be important if epileptogenic regions are closely related to functional areas.

Operation

A variety of operations can be performed, including frontal or occipital lobectomy or parietal topectomy.[13] Complications may include focal neurologic deficit due to infection, infarction, bleeding, or resection of functional areas within the epileptogenic zone.

Outcome

Few series are available for analysis, but it appears that the likelihood of becoming totally seizure free after extratemporal resection is lower than that after temporal resection.[56,57] In one series of children and adults, only 17% were seizure free after extratemporal resection, while approximately 70% had a significant reduction in seizure frequency.[57] Therefore, extratemporal resection was more often "palliative" than "curative." However, in the setting of many seizures every day, chronic drug toxicity, and a resultant plateau in neurologic development, it may be appropriate to recommend extratemporal resection with the hope of a major reduction in seizure frequency. Occasional persistent seizures after surgery may not be considered a good outcome for patients with temporal lobe epilepsy and preoperative seizure frequencies of one or two per week, but it may be an extremely gratifying outcome for an infant with extratemporal epilepsy and many seizures every day.[32]

HEMISPHERECTOMY

Selection of Candidates

Since the 1950s, hemispherectomy has been performed for patients with infantile hemiplegia and frequent, debilitating, intractable focal-onset seizures arising from multiple areas within one hemisphere.[58-64] These patients have epileptogenic areas that are too many and too extensive for focal excision of a single lobe. In patients with seizures arising from a severely damaged or malformed hemisphere, hemispherectomy may yield complete seizure control with no new neurologic deficits in addition to preexisting hemiplegia, homonymous hemianopia, and mental retardation. More recently, hemispherectomy has also been successfully performed in children with Rasmussen's focal chronic encephalitis who have progressive hemiparesis, hemispheric atrophy, and focal-onset seizures[65] and in small numbers of infants with infantile spasms and focal abnormalities seen on positron emission tomographic scans.[66]

Presurgical EEG Evaluation

Once it is clear that seizures arise from within the damaged hemisphere and that the epileptogenic zone is too extensive for a more limited cortical resection, further intensive neurophysiologic studies may not be necessary. Most patients proceed to surgery based primarily on results of scalp EEG, neuroimaging, and clinical assessment.

Operation

Early operations included en bloc removal of the entire hemisphere down to the basal ganglia.[59,61] However, in the 1970s it became clear that some patients had serious late-onset complications after hemispherectomy, with progressive neurologic deterioration and often death.[58,64] The incidence of these late complications 1 to 20 years after operation ranged from 17% to 35%, with 44% mortality.[58] The mechanism for these late complications is unclear but may be related to alteration of cerebrospinal fluid dynamics between the ventricular system and the large subdural cavity. These problems led to the development of new operative approaches,[59] including the following: (1) complete hemispherectomy with suturing of the dura mater to reduce the size of the subdural cavity[63]; (2) subtotal hemispherectomy with one or more transected cortical areas left in place as a mechanical buffer[58]; (3) hemicorticectomy, with sparing of white matter around the ventricles; and (4) complete hemispherectomy with placement of shunt tubing from the subdural cavity into the intraperitoneal space. Long-term follow-up data are so far limited to the subtotal hemispherectomies reported by Rasmussen,[58] but at least with this modification it appears that late complications are decreased with no loss of efficacy.

Outcome

Complete or near-complete seizure control after hemispherectomy is in the range of 85%.[58] This operation is therefore one of the most effective, albeit radical, forms of epilepsy surgery with regard to seizure control.

FUTURE DIRECTIONS

With the growing experience with epilepsy surgery in children, it appears that patients should be referred for consideration for possible cortical resection at specialized centers when there are intractable, disabling partial or secondary generalized seizures and focal spikes or sharp waves on EEG, with or without focal abnormalities on neuroimaging studies or neurologic examination. For selected children, a greatly improved life-style with a low risk for serious adverse effects is possible.

Many questions remain. Areas for continued research include the following: (1) better definition of the natural history of focal-onset epilepsy in infants and young children, with more longitudinal prospective follow-up studies of well-documented cases into adolescence and adulthood; (2) better understanding of the clinical and EEG findings in infants with focal-onset seizures, based on results of careful video-EEG evaluation and positron emission tomography; (3) new neuropsychologic testing methods for infants and young children to better quantify the psychosocial impact of epilepsy and epilepsy surgery; and (4) basic science investigations into the pathophysiologic mechanisms of epilepsy beginning early in life. Continued exploration in these areas will expand our understanding of optimal selection criteria and timing for epilepsy surgery in children. I thank my colleagues in the Section of Epilepsy and Clinical Neurophysiology, the Section of Pediatric Neurology, and the Department of Neurosurgery at The Cleveland (Ohio) Clinic Foundation, who have collaborated extensively in the development of the concepts behind our pediatric epilepsy surgery program.

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The Challenge of Limiting the Spread of Human Immunodeficiency Virus by Controlling Other Sexually Transmitted Diseases

Philip K. Kirby, MD; Titus Munyao, MD, ChB; Joan Kreiss, MD, MSPH; King K. Holmes, MD, PhD (*Arch Dermatol.* 1991;127:237-242)

Adipsic Hypernatremia in Two Sisters

Giorgio Radetti, MD; Francesco Rizza, MD; Giuseppe Mengarda, MD; Klaus Pittschieler, MD

• We describe two sisters with chronic hypernatremia, lack of thirst, and inappropriate osmoregulated vasopressin secretion. Only one sister, who presented with microcephaly and developmental delay, showed signs of dysplasia of the midline structures (ie, septum pellucidum and corpus callosum) and a large intracranial cyst. Neither sister showed any signs of thirst, even when osmolality exceeded 337 mmol/kg. In both patients, the vasopressin secretion did not respond to either osmotic or nonosmotic stimuli or was suppressed by a water load. Plasma osmolality values returned to normal after treatment with forced hydration and a vasopressin analogue, desamino-D-arginine vasopressin. These findings indicate a severe defect in the hypothalamic osmoreceptors that control thirst and vasopressin secretion. To our knowledge, this is the first report of such a disorder in two sisters.

(*AJDC.* 1991;145:321-325)

Adipsic hypernatremia is an uncommon disorder caused by a defect in the osmoregulation of thirst, leading to chronic hyperosmolality of body fluids.[1] In affected patients, adipsia is often associated with an abnormality in osmoregulated vasopressin secretion.[2] Different types of intracranial lesions are usually present and are thought to have damaged the hypothalamic osmoreceptors for thirst and vasopressin secretion. We describe two sisters with inappropriate lack of thirst and vasopressin secretion in the presence of chronic plasma hyperosmolality. Only one sister had a well-defined pathologic hypothalamic lesion.

PATIENT REPORTS

PATIENT 1.—Patient 1 was born after a 36-week uncomplicated pregnancy and normal delivery. Birth weight was 2.530 kg (50th percentile), length was 47 cm (50th percentile), and head circumference was 31 cm (50th percentile). The parents were nonconsanguineous. A maternal aunt had died at the age of 3 months of an undiagnosed illness; she was microcephalic and had a cleft lip and palate. The patient was first admitted to our hospital at the age of 3 months with meningococcal meningitis. She responded well to antibiotic therapy and was discharged after 15 days. On admission, laboratory values were as follows: plasma sodium, 144 mmol/L; potassium, 4.7 mmol/L; urea nitrogen, 4.8 mmol/L; creatinine, 70 µmol/L; glucose, 4.7 mmol/L; and plasma osmolality, 277 mmol/kg. During hospitalization, electrolyte levels were always within the normal range. The patient was then readmitted at the age of 10 months because of failure to thrive. On admission, the mother indicated that since the age of 5 months her daughter had been drinking very little. Laboratory values were as follows: plasma sodium, 173 mmol/L; potassium, 5.4 mmol/L; chloride, 125 mmol/L; calcium, 2.45 mmol/L; urea nitrogen, 9.6 mmol/L; creatinine, 79 µmol/L; glucose, 4.7 mmol/L; and plasma osmolality, 334 mmol/kg (normal range, 280 to 295 mmol/kg). Urinalysis showed an osmolality of 290 mmol/kg, a specific gravity of 1008, and a pH of 5. Neither proteinuria nor glycosuria was noted. Intravenous fluid therapy for 36 hours resulted in a gradual decrease in the serum concentration of sodium (to 143 mmol/L) and plasma osmolality (to 292 mmol/kg), with no convulsions and optimal weight gain. Two days after the intravenous fluid administration was stopped, the plasma sodium and osmolality values increased to 169 mmol/L and 322 mmol/kg, respectively. Plasma renin activity was 52.65 $ng \cdot L^{-1} \cdot s^{-1}$ (normal range, 0.27 to 1.08 $ng \cdot L^{-1} \cdot s^{-1}$ µg/L per hour) and the plasma aldosterone concentration was 1900 pmol/L (normal range, 20 to 440 pmol/L). The patient never showed any sign of thirst, even when the plasma osmolality was 334 mmol/kg.

Adipsic hypernatremia was suspected, and the patient underwent an extensive evaluation of the anterior and posterior portions of the hypophysis, with special interest in vasopressin secretion.

Apart from vasopressin investigation, all endocrinologic investigations were performed when the patient had good metabolic control (see "Materials and Methods" section).

Levels of serum prolactin and thyroid hormones and the thyrotropin response to thyrotropin releasing hormone were all within the normal range, as were growth hormone, cortisol, and corticotropin responses to insulin-induced hypoglycemia. Gonadotropin response to gonadotropin-releasing hormone was not tested because of the patient's young age.

Computed tomography of the skull and magnetic resonance imaging showed no parenchymal abnormalities. After water metabolism investigations were completed, the patient was discharged while receiving intranasal desamino-D-arginine vasopressin (DDAVP) (0.05 mL twice daily) and forced hydration. Although this allowed the child to grow and gain weight, every minor illness was accompanied by a recurrence of hypertonic dehydration and the need for hospitalization. The child is now 3 years old and is mentally normal.

PATIENT 2.—Patient 2, the sister of patient 1, was the product of an uncomplicated full-term pregnancy. Birth weight was 3.350 kg (50th percentile), length was 50 cm (50th percentile), and head circumference was 32 cm (10th percentile); in addition to microcephaly, a cleft lip and palate were evident.

The patient was admitted to our hospital at the age of 4 months because of seizures. Head circumference at that time was below the third percentile (37.5 cm), while the length and weight were still at the 50th percentile. The serum biochemical profile was as follows: sodium, 159 mmol/L; potassium, 4.9 mmol/L; chloride, 119 mmol/L; creatinine, 44 µmol/L; glucose, 4.7 mmol/L; calcium, 2.52 mmol/L; urea nitrogen, 8.9 mmol/L; bicarbonate, 17 mmol/L; and plasma osmolality, 309 mmol/kg. The urine specific gravity was 1005, osmolality was 120 mmol/kg, pH was 5, and no proteinuria or glycosuria was detected. Like her sister, she showed no sign of thirst.

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From the Department of Pediatrics (Drs Radetti, Mengarda, and Pittschieler) and the Laboratory Unit (Dr Rizza), Regional Hospital of Bolzano (Italy).

Reprint requests to the Department of Pediatrics, Regional Hospital, via Lorenz Boehler 5, 39100 Bolzano, Italy (Dr Radetti).

Laboratorty Values at Varying States of Hydration*

State of Hydration	Plasma Sodium, mmol/L	Plasma Urea Nitrogen, mmol/L	Plasma Osmolality, mmol/kg	Urine Osmolality, mmol/kg	Plasma Vasopressin ng/L	PRA, ng·L^{-1}·$^{-1}$	Aldosterone, pmol/L	Specific Gravity
Ad libitum A	155	5.7	298	110	3.5	8.1	600	1005
Water loading	149	7.1	299	123	2.50	8.37	800	1006
Ad libitum B	167	11	335	186	1.50	20.79	1200	1010
Normal Range	135-143	1.8-7.1	280-295	See text	See text	0.27-1.08	20-440	1002-1030

PRA indicates plasma renin activity; ad libitum A, ad libitum fluid intake on admission; and ad libitum B, fluid intake after a water load and discontinuation of hydration, when body weight decreased by more than 5%.

Antibodies against rubella, herpesvirus, *Toxoplasma*, *Treponema pallidum*, or cytomegalovirus were not detected. Karyotype was 46,XX. The electroencephalogram showed a hypsarrhythmic pattern. Computed tomography of the brain revealed dysplasia of the septum pellucidum and corpus callosum and a large cyst occupying the third and lateral ventricles. Magnetic resonance imaging confirmed these findings.

Adipsic hypernatremia was suspected, and a full endocrinologic evaluation of the anterior and posterior portions of the hypophysis was performed.

The total serum thyroxine concentration was 120 nmol/L (normal range, 56 to 154 nmol/L), free thyroxine concentration was 12 pmol/L (normal range, 9.2 to 28.3 pmol/L), triiodothyronine concentration was 1.7 nmol/L (normal range, 0.8 to 2.7 nmol/L), free triiodothyronine concentration was 4.5 pmol/L (normal range, 3.8 to 9.2 pmol/L), and reverse triiodothyronine concentration was 0.54 nmol/L (normal range, 0.14 to 0.54 nmol/L). The thyrotropin responses to an injection of 100 µg of thyrotropin releasing hormone were 1.6, 23.3, 24.7, and 25.8 mU/L at 0, 20, 40, and 60 minutes, respectively. The thyrotropin value did not return to baseline, which was interpreted as a sign of hypothalamic dysfunction. The serum prolactin level was normal, as were the responses of growth hormone, cortisol, and corticotropin to insulin-induced hypoglycemia. After water metabolism studies were completed, the patient was discharged while receiving intranasal DDAVP (0.05 mL twice daily) and forced hydration. With this regimen, satisfactory growth and weight gain were achieved, but every minor illness led to dehydration and the need for hospitalization.

At the age of 12 months, a diagnosis of West syndrome was made; at 2 years of age, the patient is severely mentally retarded.

MATERIALS AND METHODS

Informed parental consent was obtained for all the investigations performed. The patients were on an unrestricted diet and were taking no medications. For vasopressin determination, blood was collected from the antecubital vein into a chilled tube containing edetic acid, and 500 kallikrein inactivating units of aprotinin (Trasylol) was added per milliliter of blood; the blood was centrifuged at 4°C and stored at −20°C. The assay was performed within 2 months by radioimmunoassay with a commercial kit (Clonesystem, Euro Diagnostic, Apeldoorn, Holland). The assay is calibrated against the first World Health Organization Standard, 77/501: 410 IU/mg (1 ng of antidiuretic hormone per liter is equal to 0.41 µIU/mL). In a group of control patients, vasopressin values of up to 8 ng/L were found. The sensitivity of the assay is 0.8 ng/L. The plasma and urine osmolalities were calculated from the following formula: osmolality = 1.86 × (sodium + potassium) + (glucose/18) + (urea nitrogen/2.8). Blood samples for the determination of plasma renin activity and aldosterone concentration were added to edetic acid, placed on ice, centrifuged, and stored at −20°C until assay. The Diagnostic Products Corp (Los Angeles, Calif) and the SORIN (SORIN Biomedica, Saluggia, Italy) commercial kits were used for the determination of aldosterone values and renin activity, respectively. Growth hormone, cortisol, thyrotropin, prolactin, corticotropin, triiodothyronine, thyroxine, free triiodothyronine, free thyroxine, and reverse triiodothyronine levels were determined by standard radioimmunoassays.

Patient 1.—To test osmoreceptor function, during the first 2 hours, 20 mL/kg of a 5% dextrose solution was administered intravenously, followed by an additional 16 mL/kg in the third hour. During the test, 100 mL of water was administered orally to sustain diuresis. On a separate day, 0.85 mol/L of saline solution was infused at a rate of 0.05 mL/kg per minute for 3 hours.

During both tests, blood was taken from the opposite arm at 30-minute intervals for determination of plasma renin activity, plasma aldosterone concentration, vasopressin secretion, plasma osmolality, and sodium concentration. Urine specimens were also collected at the same time, via a catheter, for determination of osmolality, sodium level, and potassium level.

To test baroreceptor function, on a separate day, the effect of orthostasis on vasopressin secretion was studied while the patient was receiving 5% dextrose solution (150 mL/kg per day) intravenously for the previous 24 hours to achieve adequate hydration. At 9 AM, after basal samples of blood and urine were obtained while the patient was in the recumbent position, the patient was allowed to stand and walk, and samples of blood were taken hourly for determination of vasopressin secretion, plasma renin activity, plasma aldosterone level, sodium level, potassium level, and plasma osmolality. At the same time, urine specimens were collected for determination of osmolality and sodium and potassium concentrations. To maintain adequate diuresis, 20 mL/kg per hour of water was administered orally. Blood pressure was monitored at 30-minute intervals.

Other endocrine investigations were performed when the child was in a stable condition. We determined the response of vasopressin to other nonosmotic stimuli, such as insulin-induced hypoglycemia (during the insulin tolerance test) and emesis (15 mL of ipecac syrup given orally and blood samples taken every 10 minutes for 40 minutes).

Patient 2.—Due to the younger age of this patient, it was impossible to perform the same investigations as were performed in patient 1. Values of serum electrolytes, urea nitrogen, plasma and urine osmolality, plasma renin activity, plasma aldosterone, vasopressin, and urine specific gravity were measured during different states of hydration (Table): first on admission, when the patient was receiving fluids ad libitum, and then after a water load (intravenous infusion for 2 days with 100 mL/kg of 5% dextrose with 0.25% saline solution and forced oral hydration), and also after hydration was discontinued and body weight decreased by more than 5%.

RESULTS

Patient 1.—During the water load (Fig 1), plasma renin activity decreased from 58.32 to 27 ng·L^{-1}·s^{-1}, plasma aldosterone level decreased from 2000 to 500 pmol/L, sodium level decreased from 180 to 159 mmol/L, and osmolality decreased from 350 to 337 mmol/kg, while vasopressin secretion did not change (3.6 ng/L before water loading and 3 ng/L after water loading). Plasma vasopressin concentrations in relation to plasma osmolality were greatly reduced compared with normal values.[1] Urine osmolality at the beginning of the test was 387 mmol/kg, and specific gravity was 1017. Excretion of water load was delayed 180 minutes, at which time urine osmolality was 200 mmol/kg and specific gravity was 1009.

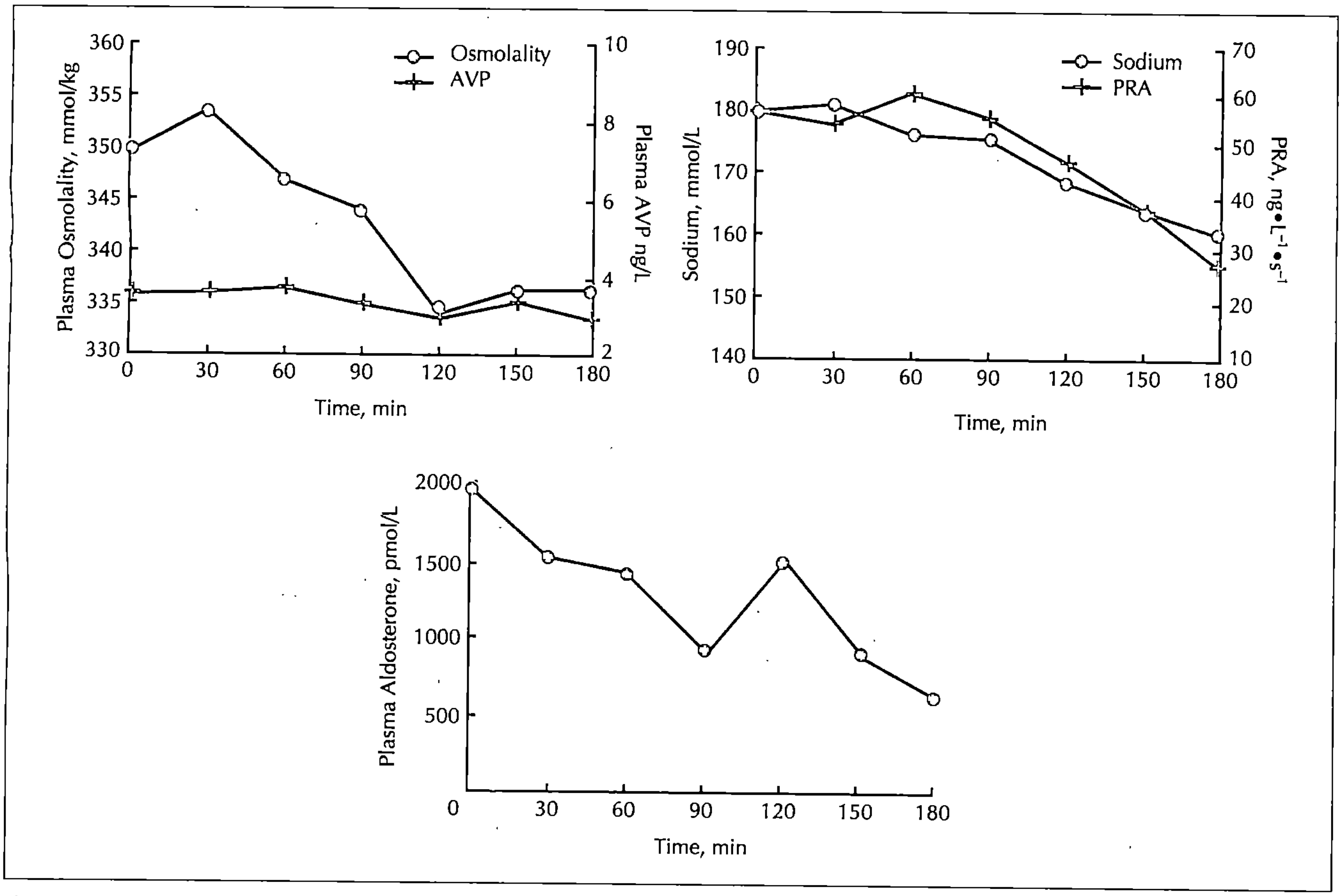

Fig 1.—*Plasma osmolality, vasopressin (AVP), sodium, plasma renin activity (PRA), and aldosterone values during water loading.*

During saline infusion (Fig 2), plasma renin activity and plasma aldosterone level decreased from 12.15 to 8.77 $ng \cdot L^{-1} \cdot s^{-1}$ and from 500 to 200 pmol/L, respectively, in response to volume expansion, while sodium level and plasma osmolality increased from 153 to 165 mmol/L and from 302 to 326 mmol/kg, respectively. Vasopressin excretion decreased from 5.2 to 3.9 ng/L. Urinary excretion of sodium began at 180 minutes. Urine specific gravity and osmolality were 1002 and 224 mmol/kg, respectively, at the beginning of the test and 1002 and 248 mmol/kg, respectively, at the end of the study.

During orthostasis (Fig 3), plasma renin activity and plasma aldosterone level increased from 15.66 to 22.95 $ng \cdot L^{-1} \cdot s^{-1}$ from 400 to 600 pmol/L, respectively; sodium level and plasma osmolality remained unchanged, as did vasopressin secretion, which was 5 ng/L at the beginning of the test and 4.2 ng/L at the end. Urinary osmolality ranged between 72 and 56 mmol/kg.

Other endocrine investigations were also performed. During the insulin-induced hypoglycemia, the vasopressin concentration increased from 3.9 to 5.2 ng/L, which is negligible after the administration of ipecac syrup, however, this value remained unchanged (from 2 to 2.8 ng/L).

Patient 2.—When patient 2 (Table) was receiving ad libitum fluid intake, the plasma sodium level ranged from 155 to 167 mmol/L; osmolality, from 298 to 335 mmol/kg; urea nitrogen level, from 5.7 to 11 mmol/L; plasma renin activity, from 8.1 to 20.79 $ng \cdot L^{-1} \cdot s^{-1}$; and plasma aldosterone, from 600 to 1200 pmol/L. Plasma vasopressin concentration was 3.5 and 1.5 ng/L, a very low value for the corresponding osmolality.[1] Concurrent urine specific gravity and osmolality were always very low compared with plasma osmolality, ranging from 1005 to 1010 and from 110 to 186 mmol/kg, respectively. The more normal biochemical measurements observed while the patient was receiving fluids ad libitum were obtained on the first day of admission, making it possible that the parents forced the child to drink at home due to fear of dehydration. We believe that the state during which fluid intake was ad libitum after a water load and discontinued hydration, as described above, reflects a more accurate basal state, as it occurred during hospitalization.

After a water load, the plasma sodium level was 149 mmol/L, osmolality was 229 mmol/kg, plasma renin activity was 8.37 $ng \cdot L^{-1} \cdot s^{-1}$, plasma aldosterone level was 800 pmol/L, urea nitrogen level was 7.1 mmol/L, and vasopressin concentration was 2.5 ng/L. Concurrent urine specific gravity was 1006 and urine osmolality 123 mmol/kg.

Investigations were also performed in the parents. Serum electrolyte levels, plasma renin activity, plasma aldosterone level, plasma osmolality, urine osmolality, and specific gravity measured in the basal state were normal. A computed tomographic scan of the skull was also normal in both parents.

COMMENT

Adipsic hypernatremia is an uncommon disease associated with a lack of thirst and often with an abnormal secretion of vasopressin. The disease includes four degrees of severity, as reviewed recently by Baylis and Thompson,[3] that are based on the thirst patterns and vasopressin secretion following an infusion of hypertonic saline solution.

In the most severe form, which is probably due to the complete destruction of hypothalamic osmoreceptors,

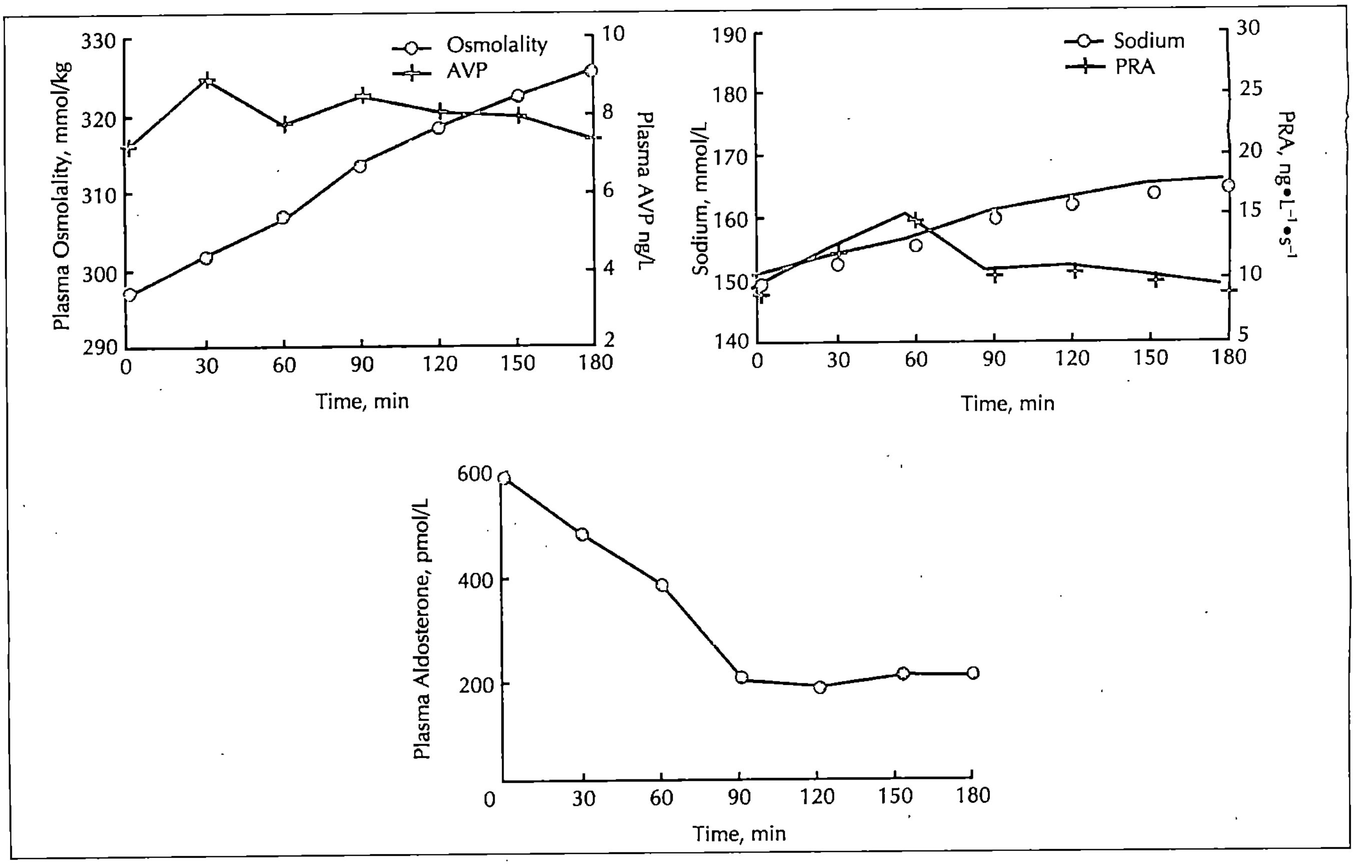

Fig 2.—*Plasma osmolality, vasopressin (AVP), sodium, plasma renin activity (PRA), and aldosterone values during hypertonic saline solution infusion.*

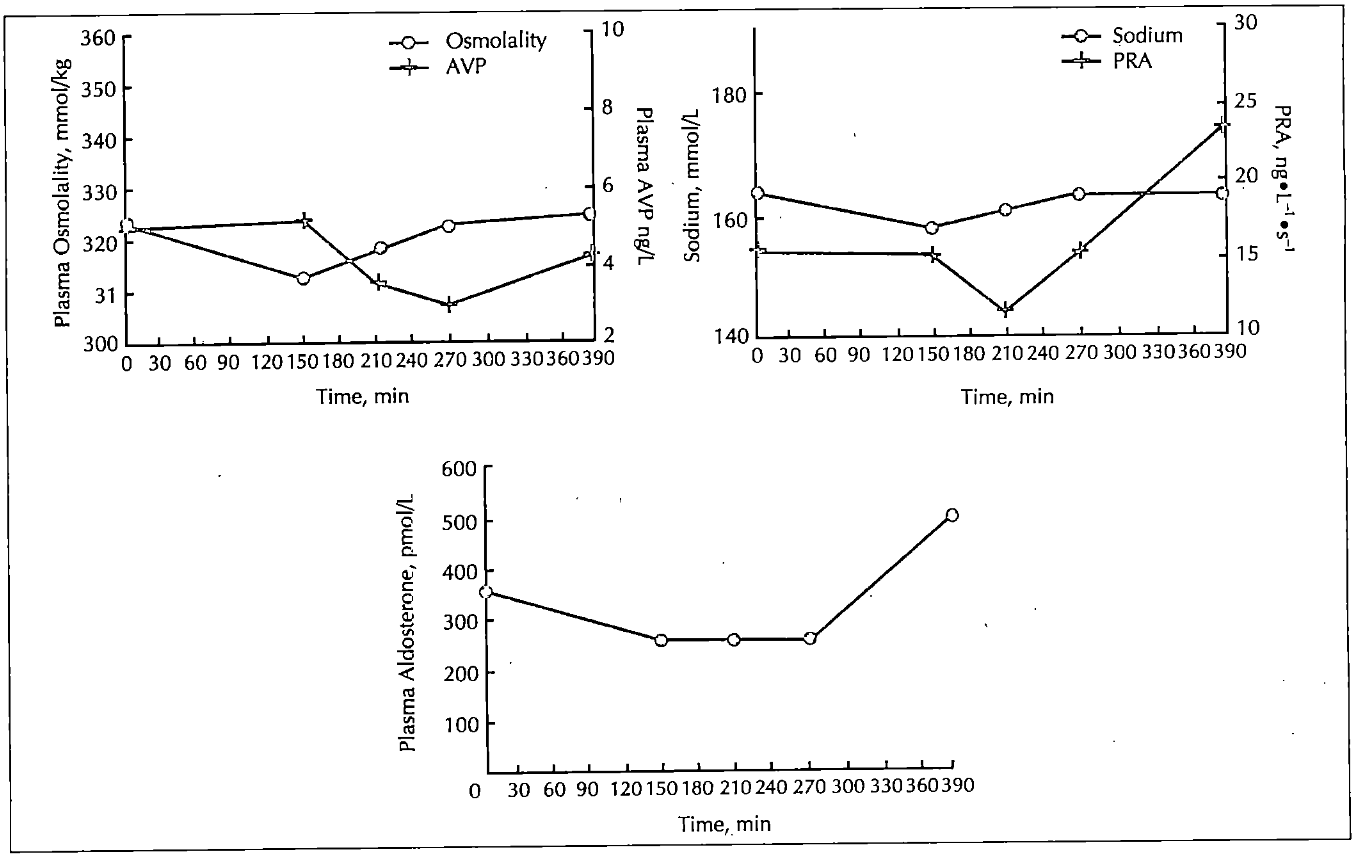

Fig 3.—*Plasma osmolality, vasopressin (AVP), sodium, plasma renin activity (PRA), and aldosterone during baroreceptor stimulation.*

neither thirst nor vasopressin response occurs irrespective of plasma osmolality; vasopressin is secreted continuously, albeit in small quantities. Herein, we describe two sisters with adipsic hypernatremia. In only one of these sisters could a diffuse alteration of the brain structure be found.

In these two patients, the lack of thirst was evident both in basal conditions and in response to osmotic stimuli, irrespective of plasma osmolality. It is well known that an increase in plasma osmolality to greater than 300 mmol/kg leads to severe thirst[4]; however, this never occurred in our patients.

Basal vasopressin secretion was evaluated in both patients and was always inappropriately low for the corresponding level of plasma osmolality.[1] A water load failed in both patients to further suppress the vasopressin secretion, and osmotic stimuli had no effect on vasopressin secretion. Moreover, following hemodynamic stimuli during orthostasis in patient 1, no response of plasma vasopressin was shown, even if the test was appropriate in light of the increase in plasma renin activity and aldosterone level. The response of vasopressin to nonosmotic stimuli such as hypoglycemia[5] (in both patients) and emesis[6] (only in the older sister) was then investigated with a negligible response. We conclude that, in our patients, vasopressin is continuously secreted and that it is neither stimulated by osmotic and nonosmotic stimuli nor suppressed by a water load. We therefore believe that both sisters suffer from the most severe form of adipsic hypernatremia; in our patients, nonosmotic stimuli had no effect on vasopressin secretion, contrary to previously reported cases.[7]

Urine osmolality was always very low in both patients when compared with plasma osmolality and especially the plasma vasopressin level.[1] In patient 1, urine osmolality never rose above 312 mmol/kg, although the vasopressin value was as high as 5.2 ng/L, which would normally cause maximal antidiuresis.[1] In patient 2, when the plasma vasopressin concentration was 3.5 ng/L, we found a corresponding urinary osmolality of only 110 mmol/kg.

We could speculate that some kind of peripheral resistance to endogenous vasopressin was present, which is supported by the normal urinary osmolality values found in both sisters (610 mmol/kg in patient 1 and 362 mmol/kg in patient 2) after the initiation of therapy with the synthetic analogue DDAVP, together with a normal plasma osmolality.

There are two possible explanations for this: either the vasopressin assay was not sufficiently sensitive or the patients' vasopressin was radioimmunologically but not biologically active, probably due to an abnormal molecule. It is also possible that antibodies to vasopressin were present, which could interfere with the radioimmunologic assay.

Adipsic hypernatremia is a rare disorder that is due to a defect in the hypothalamic osmoreceptors for thirst and vasopressin, which, to our knowledge, has not previously been reported within the same family. The sisters were affected by the same disease, although apparently caused in different ways: in the first patient, the symptoms appeared abruptly 2 months after the onset of meningitis, while in the second patient the disease was apparently due to diffuse brain abnormalities. The family history was remarkable for a maternal aunt who died at 2 months of age of an unknown disease and who had a cleft lip and palate and microcephaly, making her case very similar to that of patient 2.

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Anergy in Pediatric Head Trauma Patients

Nevin W. Wilson, MD; Ann Gooding, MD; Bradley Peterson, MD; John F. Bastian, MD

• To assess cellular immune function in children following severe blunt trauma, 25 children (mean: age, 7.1 years; Injury Severity Score, 34.9; and Glasgow Coma Score, 5.6) admitted with severe trauma were examined with the use of the CMI Multitest system (Merieux Institute, Miami, Fla) to test delayed-type hypersensitivity. Patients were monitored for evidence of infection for the next 3 weeks. Ten children (mean: age, 6.2 years; Injury Severity Score, 31.2; and Glascow Coma Score, 5.4) admitted with severe trauma had the percentage of circulating lymphocyte subpopulations (pan–T cell marker T101, CD4, CD8, and B cells) measured on day 1 and then weekly for 3 weeks. Fourteen (56%) of the 25 children had no reaction to any of the skin tests (anergic). Eleven (79%) of 14 anergic patients became infected, while three (27%) of 11 of the nonanergic children became infected. There were no significant changes in pan–T cell marker T101, CD4, or CD8 lymphocyte populations in the 3 weeks following injury; however, absolute numbers of circulating B cells dropped significantly by day 7. These data indicate that children with severe trauma who are anergic are significantly more susceptible to infection. Unlike the results reported previously in adult trauma patients, these children had no significant fluctuations in T-cell populations; however, there was a significant decrease in circulating B cells in the first week. The use of the delayed-type hypersensitivity skin test can aid in identifying which patients are at an increased risk for nosocomial infection.

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Infection is one of the major complications of severe trauma and is a primary cause of prolonged hospitalizations and death among these patients.[1] Suppression of the immune system after major blunt trauma has been implicated in adults as a cause of increased secondary infection.[2] In children, blunt trauma is responsible for more than 80% of the serious injuries,[3] with head injuries occurring more often in children than adults.[4] Additionally, there are notable differences in the immune function of young children when compared with adults. While there has been extensive research concerning the response of the immune system after severe thermal and nonthermal trauma in adults, very little information is available on severely injured children.

Measurement of delayed-type hypersensitivity (DTH) to commonly encountered antigens is a well-accepted method of assessing cell-mediated immunity.[5,6] Evaluation of DTH has been used to predict immunologic failure in adult trauma patients.[7] In this study, we describe the effect of severe head injury on circulating T cells, B cells, and T-cell subsets, as well as the use of the DTH skin test, to predict the risk of infection in critically injured children.

PATIENTS

All children in these studies were kept paralyzed with nondepolarizing muscle relaxants and sedated with fentanyl citrate while they were intubated. All children had central venous catheters, arterial catheters, and intracranial pressure monitors placed. Techniques used for the management of increased intracranial pressure included hyperventilation, mannitol treatment, and, for some patients, thiopental sodium (Pentothal). None of the children received steroids.

The protocol for this study was approved by the Children's Hospital–San Diego (La Jolla, Calif) Institutional Review Board, and written informed consent was obtained from each family.

DTH Skin Tests

Delayed-type hypersensitivity skin tests were placed on 25 children between the ages of 2 and 14 years (mean age, 7.1 years) who were admitted to the intensive care unit (ICU) at Children's Hospital–San Diego with a diagnosis of major trauma. Criteria for admission to the study included a Trauma Score less than 15 and Injury Severity Score (ISS)[8] greater than 15. The mean ISS for these patients was 34.9 (range, 17 to 50); the mean Glascow Coma Score was 5.6 (range, 3 to 11). An ISS score of 30 has a predicted mortality of 20%. Severe head injuries were the primary trauma in all 25 children. All children had immunization histories that were up to date for age. Controls consisted of 10 children (mean age, 5.5 years) who were seen in the clinic for an allergic or upper respiratory tract disorder.

T- and B-Cell Enumeration

T- and B-cell numbers were obtained on 10 children between the ages of 2 months and 14 years (mean age, 6.2 years) who were admitted with a diagnosis of major trauma. They were enrolled into the study within 36 hours of admission to the ICU (day 1). The mean ISS for these patients was 31.2 (range, 17 to 48), and the mean Glascow Coma Score was 5.4 (range, 3 to 9). Severe head injuries constituted the primary trauma in all 10 of these children.

METHODS

DTH Skin Tests

Delayed-type hypersensitivity skin reactions were measured with the use of the CMI Multitest (Merieux Institute, Miami, Fla). This is a plastic disposable puncture device that simultaneously applies seven antigens and a negative glycerin-saline control. The seven antigens were tetanus, diphtheria, *Streptococcus*, tuberculin, *Candida*, *Trichophyton*, and *Proteus*. This device has been

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From the Division of Pediatric Immunology and Allergy, Department of Pediatrics, University of California–San Diego, La Jolla (Dr Wilson), and the Divisions of Critical Care (Drs Gooding and Peterson) and Allergy and Immunology (Dr Bastian), The Children's Hospital and Health Center, San Diego, Calif.

Reprint requests to Division of Pediatric Immunology and Allergy, Department of Pediatrics/0609D, University of California–San Diego, La Jolla, CA 92093 (Dr Wilson).

Table 1.—Types of Infections

Infection	No.
Anergic patients	11
Sepsis	
Pseudomonas	1
Staphylococcus aureus	1
Candida albicans	1
Pneumonia–tracheal aspirate	
Staphylococcus epidermidis	5
Haemophilus influenzae	4
Candida species	3
S aureus	3
Pseudomonas species	2
Pneumococcus	1
Sinusitis	3
Stomatitis	
Herpes simplex virus	1
Nonanergic patients	3
Brain abscess	
Enterococcus	1
Meningitis	
Streptococcus viridans	1
Cellulitis	1
Pneumonia–tracheal aspirate	
Klebsiella	1
No organism	1

shown to assess DTH accurately in normal infants and preschool-age children.[9] This device was placed on the volar surface of one forearm within 24 hours of admission to the ICU. Skin induration was measured in two perpendicular dimensions with the use of calipers at 24 and 48 hours. All measurements were made by one observer (N.W.W.). Only reactions that were 2 mm or larger were considered to be positive. Anergy was defined as an absence of expression of DTH skin test reactivity to any of the antigens tested.[5]

Criteria for infection were defined as follows: (1) pneumonia—new or changing infiltrates on a chest roentgenogram with evidence of a systemic inflammatory response (temperature, >39°C; and leukocytosis); and (2) sepsis—positive blood culture for a commonly accepted pathogen with clinical evidence of sepsis, ie, as temperature greater than 39°C, hypotension, cardiovascular instability, elevated white blood cell count with increased neutrophils, or disseminated intravascular coagulation. Other infections were defined with use of criteria from the Centers for Disease Control, Atlanta, Ga.[10]

T- and B-Lymphocyte Enumeration, T-Cell Subsets, and Absolute Monocyte and Granulocyte Counts

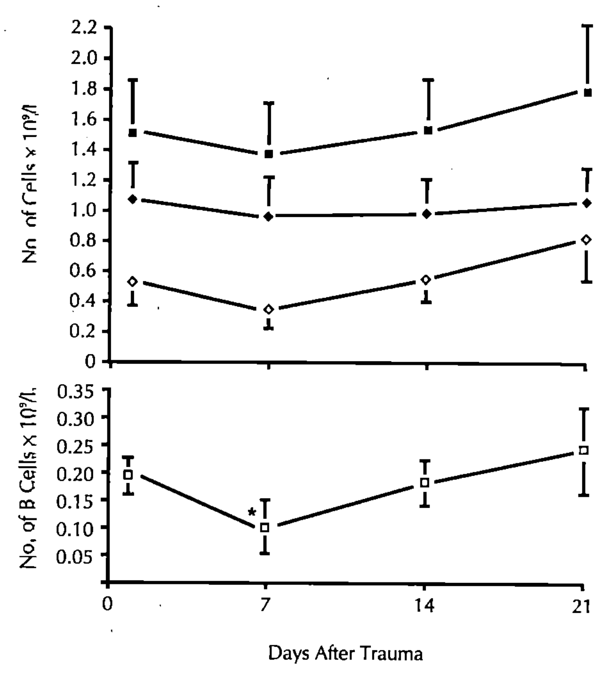
Peripheral blood, collected at 1, 7, 14, and 21 days after the injury, was diluted 1:2 in phosphate-buffered saline solution and then placed over equal amounts of Ficoll-Hypaque (Pharmacia Laboratories, Piscataway, NJ). This was centrifuged for 15 minutes at 400*g*. The peripheral blood mononuclear cells were collected at the interface and then washed with RPMI 1640 with glutamine medium (Cell Culture Facility, University of California–San Diego) two times.

T-cell subsets were analyzed with standard methods,[11] by using monoclonal antibodies to pan–T cell marker T101 (Hybritech Inc, San Diego, Calif) and CD4 and CD8 that were obtained from a manufacturer (Becton Dickinson & Co, Mountain View, Calif). B lymphocytes were identified with the use of polyclonal goat $F(ab')_2$ anti–human immunoglobulins antibody (Tago, Burlingame, Calif). The peripheral blood mononuclear cells were counted on a flow cytometer (Ortho Immunology Systems, Westwood, Mass).

Absolute numbers of monocytes and granulocytes were monitored at 1, 7, 14, and 21 days after the injury.

RESULTS

Fourteen (56%) of the 25 children met criteria for at least one infection. Three patients died: two of complications of pneumonia and one of increased intracranial pressure. There were 13 patients with pneumonia, three patients with documented sepsis, three patients with sinusitis, one patient with meningitis, one patient with a brain abscess, one patient with cellulitis, and one patient with herpes simplex stomatitis. Infections commonly occurred 5 to 10 days after admission. Table 1 lists the types of infections that were seen in the anergic and nonanergic patients.



Changes in numbers of circulating T cells (closed squares), CD4$^+$ cells (closed diamonds), CD8$^+$ cells (open diamonds), and B cells (open squares) following trauma. Error bars signify 1 SEM; asterisk, $P = .05$ compared with that on day 1.

DTH Skin Tests

Results of DTH skin tests are shown in Table 2. There were no significant differences in age, ISS, or Glasgow Coma Score between the anergic and nonanergic patients. There was no difference between our controls and published values for the CMI Multitest in children.[9]

Fourteen (56%) of the 25 children were anergic with no reactions at either 24 or 48 hours. Eleven (79%) of 14 anergic patients became infected, while three (27%) of 11 nonanergic children became infected ($P = .013$ by Fisher's Exact Test). Anergic children averaged 17 days longer in the ICU and 31 days longer in the hospital than nonanergic children. All 11 nonanergic children reacted to tetanus toxoid. Diphtheria toxoid was the second most common positive reaction, with six of 11 children reacting.

There was a significant difference in the number of skin tests that were positive ($P = .02$ by unpaired *t* test) between the nonanergic trauma patients and controls. This suggested that all of the trauma patients had some degree of anergy.

T- and B-Lymphocyte Enumeration, T-Cell Subsets, and Absolute Monocyte and Granulocyte Counts

Changes in the absolute number of T cells, T-cell subsets, and B cells for the 10 children after trauma are shown

Table 2.—Results of DTH Skin Tests*

	Anergic Patients (n=14)	Nonanergic Patients (n=11)	Controls (n=10)	P†
Mean ± SD				
Age, y	6.5±3.5	7.8±3.2	5.5±5.5	.34
ISS	35.14±9.6	34.6±12.4	...	.9
GCS	4.86±2.9	6.55±2.7	...	.15
No. of positive skin tests	0	1.73±0.8	2.6±0.8	.02
Sum of induration, mm	0	5.55±2.77	8.6±3.7	.03
No. infected	11	3	...	.01‡
Mean ± SD				
Hospital days	66.6±52	35.4±28	...	.09
ICU days	30.6±30	13.8±14	...	.1

*DTH indicates delayed-type hypersensitivity; ISS, Injury Severity Score; GCS, Glascow Coma Score; and ICU, intensive care unit.
†By unpaired *t* test.
‡By Fisher's Exact Test.

in the Figure. There were no significant changes in percentages or absolute numbers of circulating T cells, CD4-positive cells, and CD8-positive cells or in the T4-T8 ratio during the 3-week period.

Nine of the 10 patients showed decreases in the absolute number and the percentage of peripheral blood mononuclear cells that were surface immunoglobulin positive between days 1 and 7 ($P = .05$ by paired *t* test). The number of B cells then increased at 14 and 21 days to levels similar to that of day 1.

There were no significant changes noted in the absolute monocyte count or absolute granulocyte count during the 3-week period.

COMMENT

Nosocomial infections remain a major cause of increased morbidity and mortality in the severely injured patient. Sepsis accounts for 78% of all nonneurologic deaths following nonthermal trauma in adults.[1] In one study, 42% of adults admitted to an ICU with multiple trauma experienced a secondary infection.[12] This was significantly higher than for other diagnostic categories. Breaux et al[13] reported that 12% of all pediatric patients admitted for trauma experienced infectious complications.

This high nosocomial infection rate has been attributed to suppression of the immune system following severe injury.[2] Abnormalities in cellular immune function after severe nonthermal trauma in adults include depressed DTH skin tests,[7] decreased response of lymphocytes to mitogens,[14] decreases in number of T cells and helper T cells,[15] and decreased production of interleukin 2.[16] Much less is known about the effects of severe blunt trauma on the immune system of infants and children. We have recently reported that pediatric trauma patients make an abnormally low primary antibody response to a T cell–dependent neoantigen but are able to respond with normal antibody production to recall antigens, such as tetanus and diphtheria.[17]

A DTH skin reaction is a complex series of events and requires a previously sensitized subject. It requires processing of the antigen by antigen-processing cells, such as macrophages or Langerhans cells, and then presentation of this antigen to previously sensitized T cells. Production of lymphokines by these T cells induces migration of granulocytes and mononuclear cells to the site of inflammation. These cells and various soluble factors produce the vasculitis and edema that are visible in 1 to 2 days. A defect in any of these events would produce anergy.

While anergy is a marker for increased susceptibility to infection in these patients, the relationship of anergy to susceptibility remains unknown. There may exist a causal relationship, ie, trauma causes immune deficiency, which results in an increased infection rate. There may also be a noncausal relationship. Some unknown covariate(s) may cause anergy but cause increased susceptibility by a mechanism independent of anergy. Further studies are needed to elucidate the mechanism of anergy in these patients. If a causal relationship to susceptibility is present, then correction of the defect may decrease the risk of infection.

Many adults do not respond to DTH skin tests during the posttrauma period. Meakins et al[7] studied 53 adults with blunt trauma for responses to five recall antigens at admission. Twenty-two of the 53 patients were completely anergic, with 13 of 22 patients becoming septic and three deaths. Twenty-six patients had normal responses, of whom four became septic and none died. They found that the incidence of anergy depended on age and the extent of trauma. Hoyt et al[18] placed CMI Multitests on 30 adults with blunt trauma and found all 30 to be anergic. Our results are different probably because of the much shorter time period between the last immunization and testing. In our study, tetanus and diphtheria antigens were, by far, the most common positive tests in both the patients and controls.

Unlike the results that we have reported in traumatized children, adults have been shown to have decreases in the numbers of circulating T cells, as well as shifts in the T4-T8 ratio.[18] O'Mahony et al[14] studied 31 adults (mean: age, 31 years; ISS, 22) with multiple trauma and found significant decreases in circulating CD3-positive cells, as well as increases in CD8-positive cells, in the first 2 weeks after trauma.

Until recently, it has been generally thought that the effects of severe blunt trauma on intrinsic B-cell function were minor when compared with the effect on T cells.[2] Few studies have examined changes in circulating B-lymphocyte populations. Hoyt et al[18] reported no significant changes in the lymphocyte surface marker B1 in 30 adults following blunt trauma. Faist et al[19] also showed no decrease in the number of circulating B cells, but did demonstrate a decrease in the number of B cells that bore cytoplasmic immunoglobulin following injury. This suggested that impaired terminal B-cell maturation into plasma cells occurs after severe trauma in adults.

Various strategies have been proposed to help reduce the nosocomial infection rate in the severely ill, mechanically ventilated patient, such as the pediatric head trauma patient. These include the prophylactic use of intravenous immunoglobulin[20] and protective isolation.[21] Since it would be less feasible to institute these measures in all such patients, the ability to predict which patients are at a higher risk for infection would be valuable. The CMI Multitest may be useful for this purpose since it is easy to use, provides reproducible results, is relatively inexpensive, and provides a battery of seven antigens and a negative control.

We conclude that there is a significant depression of DTH reactions after severe trauma in infants and children. Furthermore, this depression correlates with the subsequent development of secondary infection. Unlike the results reported previously in adult blunt trauma patients, these children had no significant fluctuation in T-cell populations; however, there was a significant decrease in circulating B cells in the first week. The use of the DTH skin test may aid in predicting which patients are at increased risk for nosocomial infection.

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Article

Endocrine Function in Children With Human Immunodeficiency Virus Infection

Lisa J. Schwartz, DO; Yolaine St Louis, MD; Richard Wu, MD; Andrew Wiznia, MD; Arye Rubinstein, MD; Paul Saenger, MD

• **We sought to determine if failure to thrive in pediatric patients with the human immunodeficiency virus could be explained based on endocrine dysfunction. Fourteen human immunodeficiency virus–infected pediatric patients, all of whom had adequate nutritional status, underwent endocrine evaluation. Growth hormone and cortisol responses to glucagon stimulation were adequate. Despite this, eight of the 12 subjects had low somatomedin C levels. Although all patients were clinically and biochemically euthyroid, 36% (5/14) demonstrated elevated baseline and peak thyrotropin levels in response to thyroid releasing hormone, suggesting a state of compensated hypothyroidism. Although the importance of these findings is unclear, it is possible that subtle alterations of thyroid regulation may contribute to failure to thrive in some pediatric patients infected with human immunodeficiency virus and may represent a potentially correctable defect.**

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The effects of the human immunodeficiency virus (HIV) are widespread and generally the result of either opportunistic infections or neoplastic processes. Endocrine involvement, though previously described, has received less attention than many other organ systems, probably because of its often subtle manifestations. In addition, most of the information available on endocrine function in HIV infection is based on either pathologic findings at autopsy[1-4] or tests of endocrine function in adult populations.[5-8] Little attention with regard to hormonal regulation has been directed toward the pediatric population infected with HIV. However, these children are often small for gestational age at birth and continue to exhibit poor weight gain and growth through infancy and childhood.[9] By assessing the hypothalamic-pituitary axis and adrenal and thyroid function, we sought to determine if hormonal deficiencies are responsible for the failure to thrive syndrome often seen in pediatric patients known to be infected with HIV.

PATIENTS AND METHODS

Subjects were selected from the group of patients followed up at the Albert Einstein College of Medicine–affiliated hospitals, Bronx, NY (n = 12), and the Interfaith Hospital, Brooklyn, NY (n = 2), who met the following criteria: (1) HIV seropositivity determined by enzyme-linked immunosorbent assay and Western blot analysis; (2) prepubertal status; (3) no active opportunistic infections or neoplastic processes when tested; (4) no known past or present endocrinopathy; and (5) no systemic therapy with glucocorticoids within 6 months of participation. All patients were classified by the Centers for Disease Control criteria for HIV infection in children.[10]

Patient characteristics are given in Table 1. Fourteen subjects (eight females and six males) were enrolled between November 1987 and August 1988. There were eight female and six male patients. Ages ranged from 6 months to 10.5 years, with a mean (±SD) of 4.8±2.8 years. The mean height was 2.23±1.2 SDs below the norm; mean weight was 1.12±1.26 SDs below the norm; and mean growth velocity was 1.84±2.34 SDs below the norm. All patients, though free of active infection when tested, were classified as P2, ie, symptomatic infection had been noted previously. Subclassifications of P2 disease states according to the Centers for Disease Control Criteria[10] are given in Table 1. Six patients were receiving intravenous gamma globulin (300 mg/kg; Cutter Immune Globulin, Cutter Biologicals, Division of Miles, Westhaven, Conn, or Sandoglobulin, Sandoz Pharmaceuticals, East Hanover, NJ) biweekly, and these subjects were tested at least 1 week after infusion.

Endocrine Assessment

All subjects underwent the protirelin stimulation test to evaluate the hypothalamic-pituitary-thyroid axis. Protirelin was administered intravenously at a dose of 7 µg/kg. Thyrotropin response was measured by radioimmunoassay (RIA) at 0, 30, 60, 90, and 120 minutes. Baseline samples were also obtained for antithyroglobulin and antimicrosomal antibodies. Thyroxine (T_4) and triiodothyronine (T_3) levels were measured by RIA.

Glucagon (0.1 mg/kg) was administered intramuscularly. Cortisol (fluorescent polarization immunoassay) and growth hormone (RIA double-antibody technique, Cambridge Medical Diagnostics, Billerica, Mass) responses were measured at 0, 60, 90, 150, and 180 minutes. Baseline somatomedin C values (Smith Kline Bioscience Laboratories, Van Nuys, Calif, and Roche Biomedical, Raritan, NJ) were obtained as well.

All subjects were assessed at baseline and at 6 months with measurement of standing height (centimeters, Harpenden Stadiometer, Seritex, Carlstadt, NJ) and weight (kilograms). Nutritional assessment included measurement of serum transferrin (RIA, Nichols Institute, San Juan Capistrano, Calif) and serum albumin levels.

Statistical analysis was performed by a two-tailed Student *t* test. Informed consent was obtained from parents or guardians

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From the Division of Pediatric Endocrinology, Department of Pediatrics (Drs Schwartz, Wu, and Saenger), and the Division of Allergy and Immunology (Drs Wiznia and Rubinstein), Albert Einstein College of Medicine, Bronx, NY; and the Department of Pediatrics (Dr St Louis), Interfaith Medical Center, Brooklyn, NY.

Reprint requests to Division of Pediatric Endocrinology, Department of Pediatrics, Montefiore Medical Center of the Albert Einstein College of Medicine, 111 E 210th St, Bronx, NY 10467 (Dr Saenger).

Table 1.—Patient Characteristics*

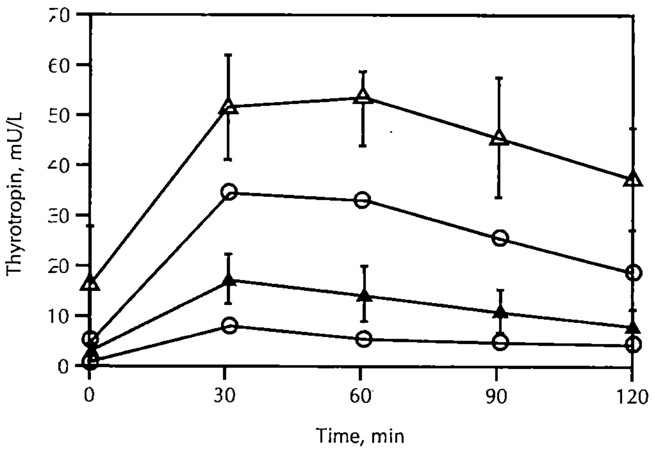
Patient No./Age, y/mo/Sex	Height	Weight	Growth Velocity	Disease Stage	Albumin, g/L	Transferrin, g/L	CD4 Count	Gamma Globulin Therapy	Somatomedin C, ng/mL
1/6/9/F	−2.5	−1.3	−4.74	P2D1	40	2.60	35	No	. . .
2/5/8/F	−3.0	−1.78	−0.70	P2B	32	2.00	112	Yes	13 (L)
3/5/10/F	−3.0	−1.23	0	P2D	35	2.65	897	Yes	13 (L)
4/5/5/F	0	0	−3.50	P2A	42	3.48	712	No	60 (N)
5/3/7/M	−1.0	+0.34	+1.30	P2D1	41	3.60	1108	Yes	19 (N)
6/2/10/F	−2.0	−1.4	−1.85	P2D1	30	. . .	774	No	0.25 U/mL (N)
7/1/10/M	−4.0	+3.3	−3.16	P2D1	35	. . .	143	No	0.52 U/mL (N)
8/6/1/F	−1.5	+1.29	−3.08	P2D1	35	3.36	10	Yes	13 (L)
9/10/4/F	−3.5	−0.9	+0.22	P2D1	30	2.43	104	Yes	22 (L)
10/4/2/F	−1.0	+.036	−2.60	P2D2	45	3.16	512	No	<5 (L)
11/3/0/M	−1.8	−1.67	+1.16	P2F	29	3.32	79	Yes	7 (L)
12/0/5/M	−3.4	−2.78	−5.80	P2A	37	2.86	212	No	7 (L)
13/10/6/M	−1.0	−1.0	−1.50	P2D2	41	3.66	280	No	95 (L)
14/1/5/M	−3.6	−2.35	−4.00	P2D1	29	. . .	479	No	. . .

*Height, weight, and growth velocity are given in SDs from the norm. For explanation of disease stages, see Centers for Disease Control.[10] Normal range for albumin is 35 to 50 g/L. Normal range for transferrin is 2.04 to 2.60 g/L. CD4 count is absolute number of T-helper lymphocytes per minute. Except for patients 6 and 7, somatomedin C values are in nanograms per milliliter. Patients 6 and 7 had values measured in a different laboratory, where they are given in units per milliliter. As normal range for somatomedin C levels are age and sex specific, each value in the table is accompanied by N (normal) or L (low).

Table 2.—Thyrotropin Response to Protirelin Stimulation Test*

Patient No.	Thyrotropin, mU/L Baseline (0 min)	Peak (30 min)	Final (120 min)
1	3.5	26.0	13.0
2	9.6	>60.0	20.1
3	2.0	17.7	3.5
4	2.2	21.2	5.4
5	3.4	25.1	4.6
6	2.0	21.2	4.8
7	36.3	>45.0	>45.0
8	<1.0	22.9	9.5
9	2.8	15.5	8.0
10	5.8	17.9	12.6
11	2.7	11.5	2.0
12	12.9	56.0	34.4
13	12.2	60.2	33.6
14	11.7	55.7	20.0

*For details of protirelin administration, see text.



Thyrotropin response to protirelin stimulation. Shaded area between circles represents range of normal values obtained in a control population. Closed triangles indicate study subjects (n = 9) with a normal protirelin response (mean±SD); open triangles, subjects (n = 5) with abnormal protirelin responses (mean±SD). See text for details.

for all subjects participating in the study. This study was approved by the institutional review board.

RESULTS

All subjects were clinically euthyroid, with normal T_3 and T_4 levels; no antimicrosomal or antithyroglobulin antibodies were detected. However, five (36%) of 14 subjects had abnormal thyrotropin responses to protirelin stimulation as defined by initial thyrotropin values greater than 5 mU/L and peak values greater than 35 mU/L.[11] These responses failed to decline to normal levels by 120 minutes after stimulation (Table 2 and Figure). When this group was analyzed separately, they were shorter (2.99±1.17 vs 1.8±1.08 cm below the norm) and had slower growth velocities (3.03±1.81 SDs vs 1.45±2.07 SDs below the norm), although the differences were not statistically significant when compared with subjects with normal thyrotropin responses.

Twelve of 14 subjects had glucagon stimulation tests. All subjects tested had adequate growth hormone responses (>10 μg/L), with a mean peak of 24.2±12.1 μg/L. In contrast, somatomedin C levels were low in eight (67%) of 12 subjects when compared with age-appropriate standards. The pituitary-adrenal axis as assessed by cortisol response to glucagon was intact in all 12, with a mean response of 830±320 nmol/L.

All subjects who had serum transferrin levels measured (n = 12) had normal values, and most had albumin levels that were normal or slightly below normal. Gamma globulin therapy did not alter hormonal responses, as those subjects receiving gamma globulin, when analyzed separately, did not demonstrate any differences.

COMMENT

Failure to thrive is a common finding in the pediatric acquired immunodeficiency syndrome. These patients are often small for gestational age and have persistent growth failure throughout infancy and childhood.[9] The general clinical status, including the persistence and severity of infection, does not consistently have a good correlation with the patient's growth.[9] Therefore, we sought to determine if the growth disturbance in pediatric patients infected with HIV could be related to hormonal dysfunction.

Endocrine complications of the acquired immunodeficiency syndrome, although not prominent features of the disease, are being increasingly recognized in adults with HIV infection. Initial attention was directed toward autopsy studies, which have demonstrated opportunistic infections and the presence of Kaposi's sarcoma in the adrenal, pituitary, and thyroid glands.[3,4,12-15]

Prompted by reports of hyponatremia, hyperkalemia, and hypotension, adrenal involvement has received the most attention to date.[16-18] Invasion by opportunistic infection, when specifically searched for, has been reported in the adrenal in up to 81% of patients examined.[3] Cytomegalovirus is the most commonly noted pathogen, found in up to 51% of patients, followed by *Mycobacterium avium-intracellulare* in 12% and *Cryptococcus* species in 7%.[3] However, the extent of adrenocortical necrosis in most of these cases has been less than 50%, which is generally considered insufficient to cause adrenal insufficiency.[3]

Investigations of adrenal function and response to corticotropin stimulation have reached conflicting conclusions. Evaluations of baseline and stimulated cortisol responses by our group as well as by Dobs et al[6] have shown them to be well within normal limits. This is in contrast to other studies, which have demonstrated either a reduction in the maximum stimulated cortisol level[19] or elevated baseline cortisol[5,20] and corticotropin[20] values when compared with control populations.

Detailed examination of mineralocorticoids has shown an impairment of the 17-deoxy pathway (corticosterone, 18-hydroxydeoxycorticosterone) on short- and long-term corticotropin stimulation, with no alteration in the end products of the pathway (aldosterone, 18-hydroxycorticosterone).

Although histopathologic abnormalities of the pituitary have been reported to be unusual,[21] involvement has been demonstrated in up to 23% of patients with HIV.[13] Again, most of these lesions are infectious in origin, although vascular anomalies, including ischemic necrosis and microthrombosis of the neurohypophyseal vessels, were seen as well.

Given these lesions of the pituitary, it is appealing to attempt to correlate the growth abnormalities in HIV-infected patients with pituitary dysfunction. An isolated case of growth hormone deficiency was reported in a 6-year, 10-month-old girl who was HIV positive and had a 2-year history of growth failure.[22] However, our data, and those of Rappaport et al,[23] could find no correlation between growth or growth velocity and hormonal measures, such as growth hormone and/or somatomedin C level.

In this study, we examined an unselected population of HIV-positive pediatric patients who had no known active opportunistic infection but demonstrated as a group short stature and abnormally low growth velocities. When we specifically examined pituitary and adrenal unresponsiveness to glucagon stimulation, we were unable to demonstrate any abnormality in growth hormone or cortisol secretion. However, despite normal growth hormone and normal visceral protein synthetic capabilities, as measured by transferrin level,[24] most of these patients had depressed somatomedin C levels. Low somatomedin C level has also been observed in patients with hemophilia and HIV infection.[25]

The thyroid gland has also been demonstrated to be involved with opportunistic infectious processes. Again, cytomegalovirus appears frequently in studies of pathologic specimens, but Kaposi's sarcoma, *Pneumocystis carinii*, and *Cryptococcus* species have also been reported.[26]

To date, evaluation of thyroid function has yielded conflicting results. Initial studies reported normal measures of thyroid function, including normal thyrotropin responses to protirelin stimulation.[6] Others, however, found changes in thyroid function commonly associated with nonthyroidal illness, ie, the sick euthyroid syndrome.[7] LoPresti et al[8] reported unique alterations in thyroid function in patients with acquired immunodeficiency syndrome: a progressive decline in reverse T_3 value and elevation in T_4-binding globulin level that accompanied advancing HIV infection. They postulated that perhaps the persistence of a normal T_3 value in the setting of a severe systemic illness may play a role in facilitating the weight loss and wasting syndrome often seen in HIV-positive patients even in the absence of an active infectious or neoplastic process.

We have found that all subjects examined in this study had normal T_3 and T_4 levels. However, we identified a subset of individuals in whom not only growth measures were abnormal, but who also manifested an abnormal thyrotropin response to protirelin stimulation. These subjects had elevated baseline thyrotropin levels with exaggerated and prolonged thyrotropin response to protirelin. We believe that this aberrant response may represent a state of compensated hypothyroidism in these children. Whether this abnormal thyrotropin response represents an earlier, more sensitive indicator for thyroidal illness than the progressive fall in T_3 and T_4 levels seen in the patients of LoPresti et al remains to be determined.

Although failure to thrive and growth disturbances characterize many pediatric patients infected with HIV, we could find no single endocrine abnormality that could be directly responsible for this. Two intriguing abnormalities were noted. The first is that of depressed somatomedin C levels in the setting of normal growth hormone secretion after pharmacologic stimulation. This may represent a state of resistance or insensitivity to the peripheral actions of growth hormone. However, it is also possibly a reflection of a chronic illness. Subtle degrees of malnutrition that we were not able to pick up with one clinical and laboratory assessment of nutritional status also may have lowered somatomedin C concentrations.[27] The second, perhaps more important, finding is a state of compensated hypothyroidism in a subset of subjects that demonstrated a trend toward slower growth velocities and shorter statures. The importance of these findings has yet to be determined, but it is conceivable that if alterations of thyroid regulation contribute to failure to thrive in some HIV-infected pediatric patients, this may represent a potentially correctable defect.

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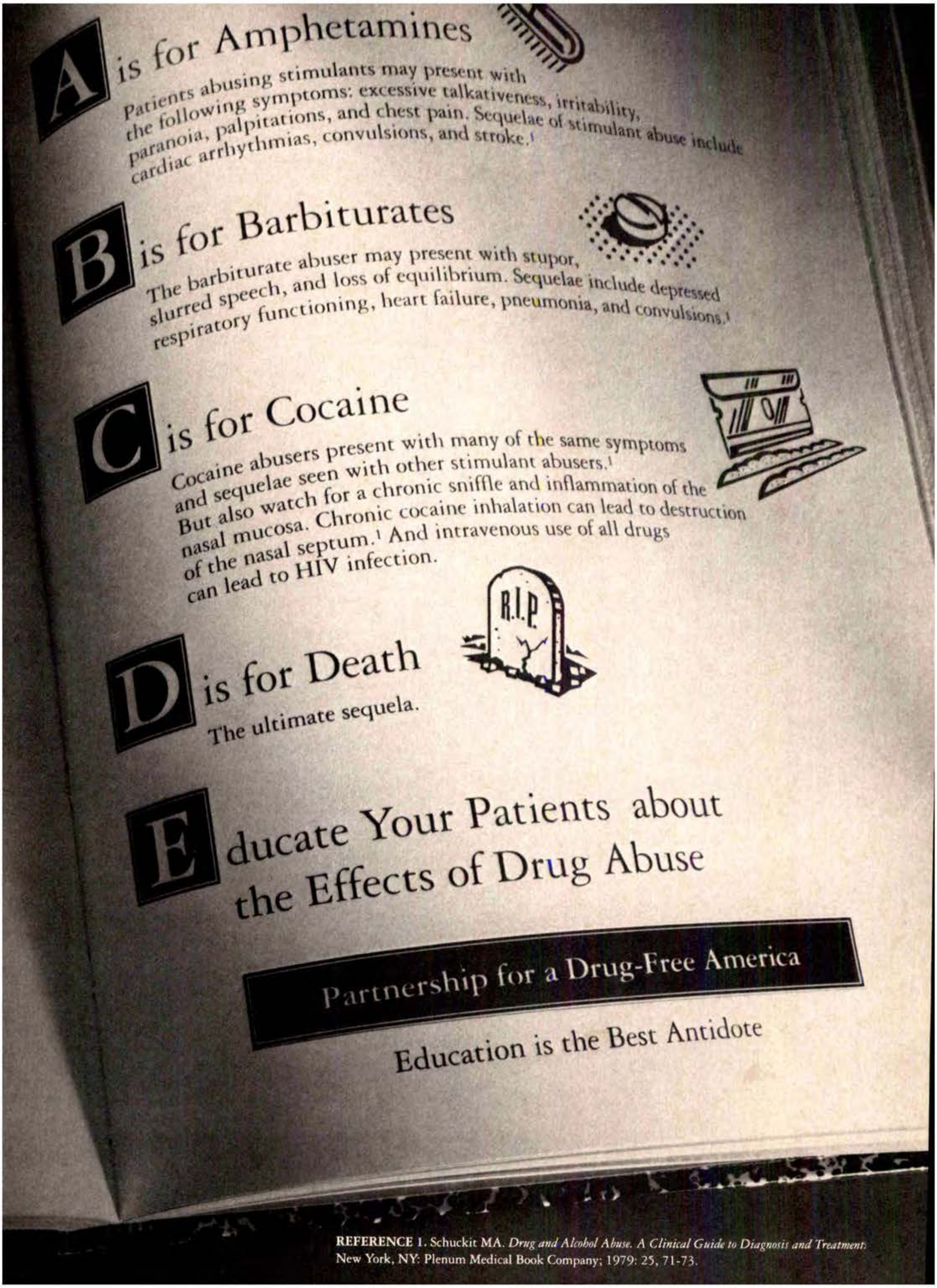

A is for Amphetamines

Patients abusing stimulants may present with the following symptoms: excessive talkativeness, irritability, paranoia, palpitations, and chest pain. Sequelae of stimulant abuse include cardiac arrhythmias, convulsions, and stroke.[1]

B is for Barbiturates

The barbiturate abuser may present with stupor, slurred speech, and loss of equilibrium. Sequelae include depressed respiratory functioning, heart failure, pneumonia, and convulsions.[1]

C is for Cocaine

Cocaine abusers present with many of the same symptoms and sequelae seen with other stimulant abusers.[1] But also watch for a chronic sniffle and inflammation of the nasal mucosa. Chronic cocaine inhalation can lead to destruction of the nasal septum.[1] And intravenous use of all drugs can lead to HIV infection.

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REFERENCE 1. Schuckit MA. *Drug and Alcohol Abuse. A Clinical Guide to Diagnosis and Treatment.* New York, NY: Plenum Medical Book Company; 1979: 25, 71-73.

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Please see brief summary of Prescribing Information on the next page.

References:
1. Walson PD et al. Ibuprofen, acetaminophen, and placebo treatment of febrile children. *Clin Pharmacol Ther.* 1989;46:9-17. 2. Data on file, McNeil Consumer Products Company.

PediaProfen™

Ibuprofen Suspension 100 mg/5 ml

The following is a brief summary only. Before prescribing, see complete prescribing information in **PediaProfen** labeling.

INDICATIONS AND USAGE: PediaProfen is indicated for the reduction of fever in patients aged 6 months and older, and for the relief of mild-to-moderate pain in patients aged 12 years and older.

CLINICAL PHARMACOLOGY: Controlled clinical trials comparing doses of 5 and 10 mg/kg ibuprofen and 10-15 mg/kg of acetaminophen have been conducted in children 6 months to 12 years of age with fever primarily due to viral illnesses. In these studies there were no differences between treatments in fever reduction for the first hour and maximum fever reduction occurred between 2 and 4 hours. Response after 1 hour was dependent on both the level of temperature elevation as well as the treatment. In children with baseline temperatures at or below 102.5°F, both ibuprofen doses and acetaminophen were equally effective in their maximum effect. In those children with temperatures above 102.5°F, the ibuprofen 10 mg/kg dose was more effective. By 6 hours children treated with ibuprofen 5 mg/kg tended to have recurrence of fever, whereas children treated with ibuprofen 10 mg/kg still had significant fever reduction at 8 hours. In control groups treated with 10 mg/kg acetaminophen, fever reduction resembled that seen in children treated with 5 mg/kg of ibuprofen, with the exception that temperature elevation tended to return 1-2 hours earlier.

CONTRAINDICATIONS: PediaProfen should not be used in patients who have previously exhibited hypersensitivity to ibuprofen, or in individuals with all or part of the syndrome of nasal polyps, angioedema and bronchospastic reactivity to aspirin or other nonsteroidal anti-inflammatory agents. Anaphylactoid reactions have occurred in such patients.

WARNINGS: Risk of GI Ulceration, Bleeding and Perforation with NSAID Therapy. Serious gastrointestinal toxicity such as bleeding, ulceration, and perforation, can occur at any time, with or without warning symptoms, in patients treated chronically with NSAID therapy. Although minor upper gastrointestinal problems, such as dyspepsia, are common, usually developing early in therapy, physicians should remain alert for ulceration and bleeding in patients treated chronically with NSAIDs even in the absence of previous GI tract symptoms. In patients observed in clinical trials of several months to two years duration, symptomatic upper GI ulcers, gross bleeding or perforation appear to occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for one year. Physicians should inform patients about the signs and/or symptoms of serious GI toxicity and what steps to take if they occur.

Studies to date have not identified any subset of patients not at risk of developing peptic ulceration and bleeding. Except for a prior history of serious GI events and other risk factors known to be associated with peptic ulcer disease, such as alcoholism, smoking, etc., no risk factors (e.g., age, sex) have been associated with increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less well than other individuals and most spontaneous reports of fatal GI events are in this population. Studies to date are inconclusive concerning the relative risk of various NSAIDs in causing such reactions. High doses of any NSAID probably carry a greater risk of these reactions, although controlled clinical trials showing this do not exist in most cases. In considering the use of relatively large doses (within the recommended dosage range), sufficient benefit should be anticipated to offset the potential increased risk of GI toxicity.

PRECAUTIONS: General: Blurred and/or diminished vision, scotomata, and/or changes in color vision have been reported. If a patient develops such complaints while receiving **PediaProfen**, the drug should be discontinued and the patient should have an ophthalmologic examination which includes central visual fields and color vision testing.

Fluid retention and edema have been reported in association with ibuprofen; therefore, the drug should be used with caution in patients with a history of cardiac decompensation or hypertension.

PediaProfen, like other nonsteroidal anti-inflammatory agents, can inhibit platelet aggregation, but the effect is quantitatively less and of shorter duration than that seen with aspirin. Ibuprofen has been shown to prolong bleeding time (but within the normal range) in normal subjects. Because this prolonged bleeding effect may be exaggerated in patients with underlying hemostatic defects, **PediaProfen** should be used with caution in persons with intrinsic coagulation defects and those on anticoagulant therapy.

Patients on **PediaProfen** should report to their physicians signs or symptoms of gastrointestinal ulceration or bleeding, blurred vision or other eye symptoms, skin rash, weight gain, or edema.

In order to avoid exacerbation of disease of adrenal insufficiency, patients who have been on prolonged corticosteroid therapy should have their therapy tapered slowly rather than discontinued abruptly when ibuprofen is added to the treatment program.

The antipyretic and anti-inflammatory activity of **PediaProfen** may reduce fever and inflammation, thus diminishing their utility as diagnostic signs in detecting complications of presumed noninfectious, noninflammatory painful conditions.

Since ibuprofen is eliminated primarily by the kidney, patients with significantly impaired renal function should be closely monitored and a reduction in dosage should be anticipated to avoid drug accumulation. Prospective studies on the safety of ibuprofen in patients with chronic renal failure have not been conducted.

Safety and efficacy of **PediaProfen** in children below the age of 6 months has not been established.

Pregnancy: Reproductive studies conducted in rats and rabbits at doses somewhat less than the maximal clinical dose did not demonstrate evidence of developmental abnormalities. However, animal reproduction studies are not always predictive of human response. As there are no adequate and well-controlled studies in pregnant women, this drug should be used during pregnancy only if clearly needed. Because of the known effects of nonsteroidal anti-inflammatory drugs on the fetal cardiovascular system (closure of ductus arteriosus), use during late pregnancy should be avoided. As with other drugs known to inhibit prostaglandin synthesis, an increased incidence of dystocia and delayed parturition occurred in rats. Administration of **PediaProfen** is not recommended during pregnancy.

ADVERSE REACTIONS: The most frequent type of adverse reaction occurring with ibuprofen is gastrointestinal. In controlled clinical trials, the percentage of adult patients reporting one or more gastrointestinal complaints ranged from 4% to 16%.

Adverse reactions occurring in 3% to 9% of patients treated with ibuprofen: nausea, epigastric pain, heartburn, dizziness, rash. *Adverse reactions occurring in 1% to 3% of patients:* diarrhea, abdominal distress, nausea and vomiting, indigestion, constipation, abdominal cramps or pain, fullness of GI tract, headache, nervousness, pruritus, tinnitus, decreased appetite, edema, fluid retention (generally responds promptly to drug discontinuation). Still other reactions (less than 1 in 100) have been reported, and are detailed in the full summary of prescribing information.

DOSAGE AND ADMINISTRATION: Shake well prior to administration.

Fever Reduction in Children 6 months to 12 years of age: Dosage should be adjusted on the basis of the initial temperature level (See CLINICAL PHARMACOLOGY for a description of the controlled clinical trial results). The recommended dose is 5 mg/kg if the baseline temperature is less than 102.5°F or 10 mg/kg if the baseline temperature is greater than 102.5°F. The duration of fever reduction is generally 6-8 hours and is longer with the higher dose. The recommended maximum daily dose is 40 mg/kg.

Mild to moderate pain: 400 mg every 4 to 6 hours as necessary for the relief of pain in adults.

In controlled analgesic clinical trials, doses of ibuprofen greater than 400 mg were no more effective than 400 mg dose.

HOW SUPPLIED: PediaProfen Ibuprofen Suspension 100 mg/5 ml (teaspoon)—
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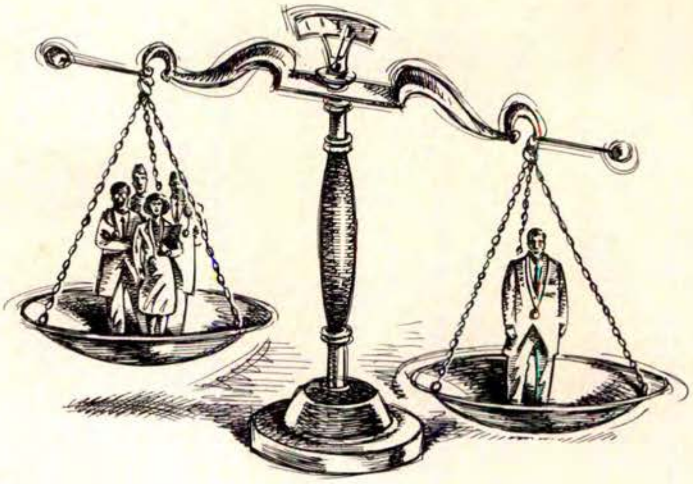

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SPECIAL FEATURE

Radiological Case of the Month

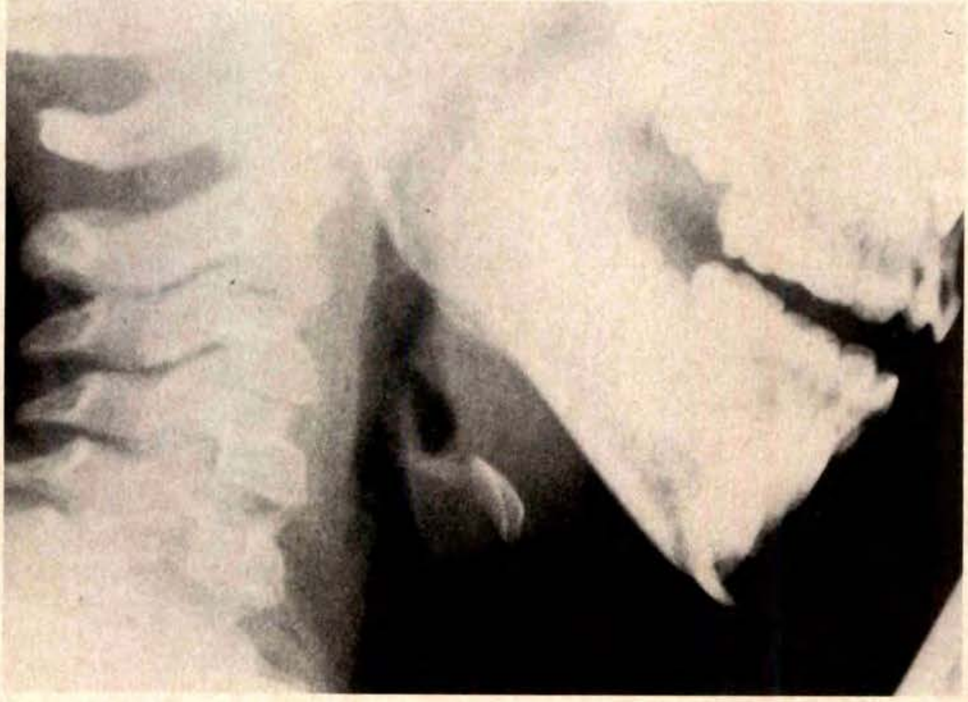
Michele K. Holloway, MD; Suman Wason, MD, MBA; J. Paul Willging, MD; Charles M. Myer III, MD (Contributors); *Beverly P. Wood, MD* (Section Editor)

A 5-year-old girl presented to the emergency department with a history of shortness of breath and coughing. Although she had been coughing for several weeks, there was an abrupt change in character and the cough became more "croupy" on the night of her presentation to the hospital. The patient complained of a "scratchy" sensation in her throat. No fever was reported.

On physical examination, the patient's vital signs were as follows: temperature, 37.2°C; pulse, 150 beats per minute; respiratory rate, 26 per minute; and blood pressure, 120/65 mm Hg. She was a well-developed child who was alert and cooperative. She was not in respiratory distress, but had a dry, croupy cough and mild inspiratory and expiratory stridor, and constantly attempted to clear her throat. The remainder of the examination findings were normal. A pulse oximeter reading showed 95% to 100% oxygen saturation in room air. Chest radiographic findings were normal.

A diagnosis of foreign body aspiration or foreign body lodged within the pharynx was entertained, although the patient denied any foreign body ingestion. A lateral neck roentgenogram was obtained (Fig 1), and reportedly demonstrated a calcified foreign body at the level of the hypopharynx. An otolaryngologist was consulted to remove the foreign body.

Figure 1.



Accepted for publication March 12, 1990.

From the Emergency Department (Drs Holloway and Wason) and the Department of Otolaryngology and Maxillofacial Surgery (Drs Willging and Myer), Children's Hospital Medical Center, University of Cincinnati, Ohio.

Reprint requests to the Department of Radiology, Childrens Hospital of Los Angeles, 4650 Sunset Blvd, Los Angeles, CA 90027 (Dr Wood).

Denouement and Discussion

A Pediatric Case of Eagle's Syndrome

Fig 1.—*Lateral neck roentgenogram showing a calcification extending from C-1 to the angle of the mandible.*

Fig 2.—*Diagram demonstrates the stylomandibular, stylohyoid ligament complex. A indicates stylomandibular ligament; and B, stylohyoid ligament.*

On review of the radiographs, we identified the "foreign body" as a calcified stylomandibular ligament. The scratchy sensation and continual clearing of the throat were symptoms associated with this calcified ligament. The patient was reassured and no therapy was administered. Incidental sinus radiograms were obtained and showed bilateral maxillary sinus opacification. The patient was given a diagnosis of chronic sinusitis and symptomatic calcified stylomandibular ligament; she was discharged while receiving amoxicillin treatment.

Eagle's syndrome is defined as the symptomatic mineralization of the stylohyoid-stylomandibular ligament complex (MSSLC).[1] The variations of the styloid process and its adjoining ligaments have been of interest to anatomists for 300 years, most recently in relation to the advent of diagnostic radiology.

Eagle reported more than 200 cases in the 1930s and 1940s and documented symptoms associated with anomalies of the styloid process. Although many patients are asymptomatic, the symptoms associated with MSSLC are related to the hypopharynx. These include dysphagia (80%), pharyngeal foreign body sensation (55%), and constant aching in the throat (40%).[2] Less common complaints include otalgia, headache, pain on turning the head, and facial pain.[3]

The styloid process is usually a small, slender, tapering projection of the temporal bone located in front of the stylomastoid foramen. It lies between the internal and external carotid arteries, posterior to the tonsillar fossa and lateral to the pharyngeal wall, with three muscles (the stylopharyngeus, stylohyoid, and styloglossus) attached to it. These are supplied by the glossopharyngeal, facial, and hypoglossal nerves, respectively. At the apex, two ligaments are inserted into the styloid. The stylohyoid ligament extends from the far end of the styloid process to the lesser cornu of the hyoid bone. The stylomandibular ligament is inserted at the angle of the apex and extends to the angle of the mandible (Fig 2).[2-5]

A radiographic survey of 4200 men aged 18 to 22 years demonstrated only a 1.4% incidence of MSSLC. None of the patients was symptomatic. In other studies, 8% to 28% of patients with MSSLC have been symptomatic. Clinically, the syndrome is usually not seen prior to age 30 years.[3] In a review of the literature by Gossman and Tarsitano,[3] only one patient younger than 30 years was found to be symptomatic. The anomaly is present more frequently in the 40- to 80-year age range, with symptoms developing after the fourth decade.[6] The etiology of the mineralization is unknown. There is no significant sex predilection in the occurrence of MSSLC[3]; however, symptoms are more common among women.[4]

The radiographic diagnosis of the MSSLC is best made with a temporomandibular joint panoramic radiograph and frontal and lateral projections of the neck to visualize the anatomy in three planes. The anomaly is bilateral and the elongated styloid process can be palpated by inserting a finger orally along the occlusal line posterior to the region of the tonsillar fossa. Pain is experienced as the elongated process is palpated. Another test is to administer regional anesthesia in the area of the tonsillar fossa for relief of symptoms.[3]

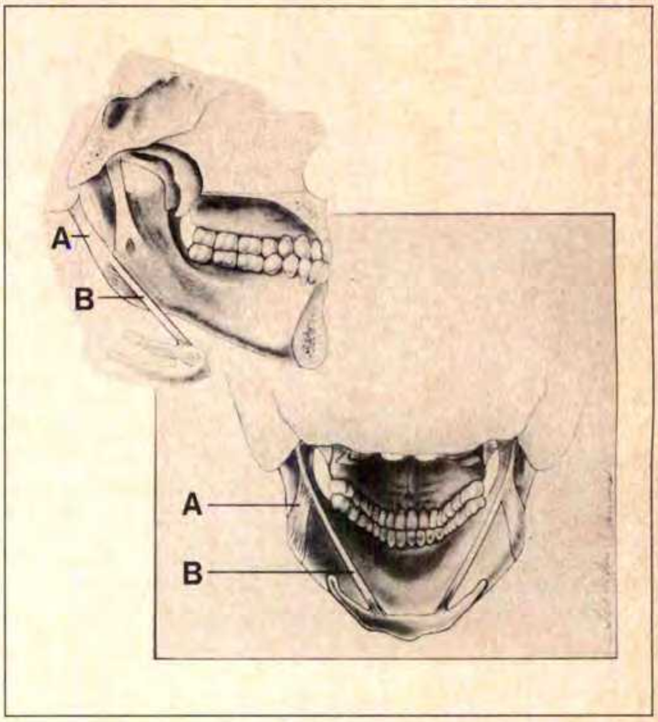


Figure 2.

The differential diagnosis of Eagle's syndrome includes impacted third molars; migrainous neuralgias; trigeminal, vagoglossal, or geniculate neuralgias; temporomandibular joint abnormalities; and psychosomatic disease.[1]

Treatment in severely symptomatic patients is surgical excision of the styloid process. Most patients require only reassurance and symptomatic treatment. Calcification of the styloid process is not an uncommon occurrence and physicians should be aware of this entity when entertaining the diagnosis of an atypical pharyngeal foreign body.

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SPECIAL FEATURE

Picture of the Month

Diane E. Friedman, MEd; Richard J. Pines, DO; Matthew Shelley, MD; Pamela Fisher, MD; G. Michael Silberbach, MD (Contributors); *Murray Feingold, MD* (Section Editor)

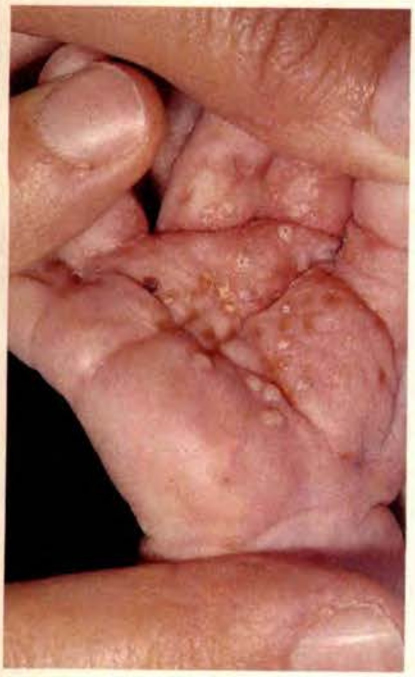
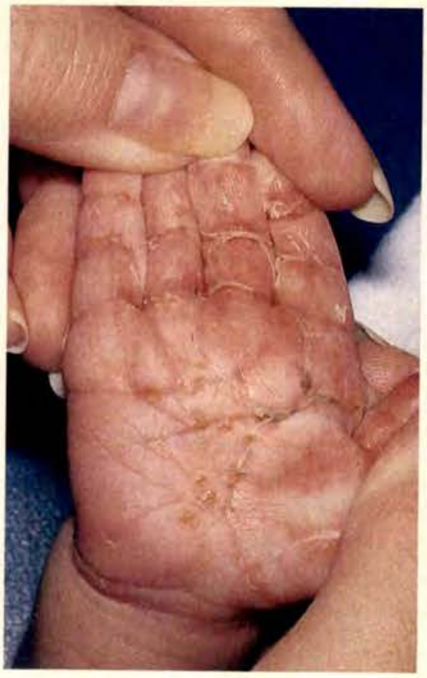


Figure 1.



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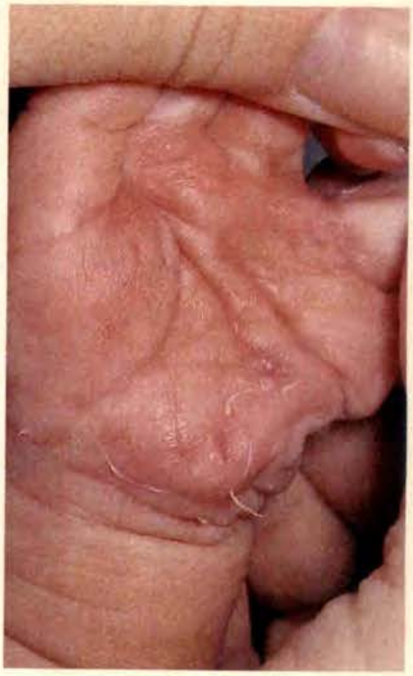
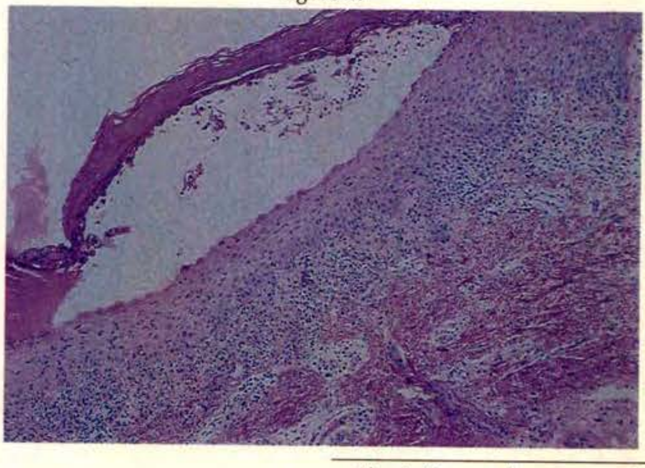


Figure 3.

Figure 4.



Accepted for publication November 3, 1990.

Contributed from the Department of Pediatrics, Oregon Health Sciences University, Portland.

Reprint requests to the National Birth Defects Center, Franciscan Children's Hospital, 30 Warren St, Brighton, MA 02135 (Dr Feingold).

The Editors welcome contributions to Picture of the Month and Radiological Case of the Month. Those who wish to contribute should send their manuscripts to Dr Feingold (Picture of the Month), National Birth Defects Center, Kennedy Memorial Hospital, 30 Warren St, Brighton, MA 02135, or Dr Wood (Radiological Case of the Month), Department of Radiology, Childrens Hospital of Los Angeles, 4650 Sunset Blvd, Los Angeles, CA 90027. Articles and photographs accepted for publication will bear the contributor's name. There is no charge for reproduction and printing of color illustrations.

Denouement and Discussion

Acropustulosis of Infancy

Fig 1.—*Hand at presentation showing circumscribed, intensely pruritic, pustular dermatitis.*

Fig 2.—*Hand 1 week after presentation showing resolving lesions with peeling skin and no pustules.*

Fig 3.—*Hand 2 weeks after presentation, with minimal peeling of the skin.*

Fig 4.—*Photomicrograph of biopsy specimen of pustule showing subcorneal accumulation of neutrophils.*

Manifestations

Acropustulosis of infancy is an uncommon but distinctive dermatosis often mistaken for pustular impetigo. The unusual cutaneous distribution is the principle distinguishing characteristic. Sterile, pruritic pustules appear mainly on the palms and soles and less frequently on the dorsum of the hands, feet, wrists, and ankles. Lesions evolve from pinpoint-sized erythematous papules that enlarge to form well-circumscribed pustules. Eruptions appear to be more severe during the summer. Onset occurs usually between ages 2 and 10 months, but the rash has been observed in newborns. Recurrences in children up to age 2 years have been reported.

Diagnosis is based on the clinical presentation and lack of response to antibiotic or antifungal therapy. Cultures of the pustules are invariably sterile unless associated with secondary infection. Histologic examination of the lesion demonstrates a circumscribed, subcorneal pustule filled with polymorphonuclear leukocytes. The floor of the pustule consists of compact keratin and the base has a compressed atrophic malpighian layer. The papillary dermis shows slight edema.

The differential diagnosis of acropustulosis of infancy includes dyshidrotic eczema, pustular psoriasis, toxic erythema of the newborn, transient neonatal pustular melanosis, infantile scabies, subcorneal pustular dermatosis, and impetigo.

Genetics

The cause is unknown. A genetic predisposition has been postulated since most cases occur in black or Asian children. Unlike other types of aseptic dermatosis, a family history of atopy or psoriasis is uncommon.

Treatment

Acropustulosis of infancy is self-limited, with no known adverse sequelae. Therapy is directed toward relieving the symptoms of pruritus and discomfort and preventing secondary bacterial infection.

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PedvaxHIB is contraindicated in patients who are hypersensitive to any component of the vaccine or the diluent.

For a Brief Summary of Prescribing Information, please see next page.

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INDICATIONS AND USAGE: PedvaxHIB is indicated for routine immunization against invasive disease caused by *Haemophilus influenzae* type b in infants and children 2 to 71 months of age.

PedvaxHIB will not protect against disease caused by *Haemophilus influenzae* other than type b or against other microorganisms that cause invasive disease, such as meningitis or sepsis.

Revaccination: Infants completing the primary two-dose regimen before 12 months of age should receive a booster dose (see DOSAGE AND ADMINISTRATION).

Use with Other Vaccines: Studies have been conducted in which PedvaxHIB has been administered concomitantly with the primary vaccination series of DTP and OPV, or concomitantly with M-M-R® II (Measles, Mumps, and Rubella Virus Vaccine Live, MSD) (using separate sites and syringes), or with a booster dose of OPV plus DTP (using separate sites and syringes for PedvaxHIB and DTP). No impairment of immune response to individual tested vaccine antigens was demonstrated. The type, frequency, and severity of adverse experiences observed in these studies with PedvaxHIB were similar to those seen when the other vaccines were given alone.

PedvaxHIB IS NOT RECOMMENDED FOR USE IN INFANTS YOUNGER THAN 2 MONTHS OF AGE.

CONTRAINDICATIONS: Hypersensitivity to any component of the vaccine or the diluent.

WARNINGS: USE ONLY THE ALUMINUM HYDROXIDE DILUENT SUPPLIED. If PedvaxHIB is used in persons with malignancies or in those who are receiving immunosuppressive therapy or who are otherwise immunocompromised, the expected immune response may not be obtained.

PRECAUTIONS: ***General:*** As for any vaccine, adequate treatment provisions, including epinephrine, should be available for immediate use should an anaphylactoid reaction occur. As with other vaccines, PedvaxHIB may not induce protective antibody levels immediately following vaccination. As with any vaccine, vaccination with PedvaxHIB may not result in a protective antibody response in all individuals given the vaccine. As reported with Haemophilus b polysaccharide vaccine and another Haemophilus b conjugate vaccine, cases of Haemophilus b disease may occur in the week after vaccination, prior to the onset of the protective effects of the vaccines. There is insufficient evidence that PedvaxHIB given immediately after exposure to natural *Haemophilus influenzae* type b will prevent illness. Any acute infection or febrile illness is reason for delaying use of PedvaxHIB except when, in the opinion of the physician, withholding the vaccine entails a greater risk.

Laboratory Test Interactions: Sensitive tests (e.g., Latex Agglutination Kits) may detect PRP derived from the vaccine in urine of some vaccinees for up to seven days following vaccination with PedvaxHIB; in clinical studies with PedvaxHIB, such children demonstrated normal immune response to the vaccine.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: PedvaxHIB has not been evaluated for its carcinogenic or mutagenic potential or for its potential to impair fertility.

Pregnancy: *Pregnancy Category C:* Animal reproduction studies have not been conducted with PedvaxHIB. It is also not known whether PedvaxHIB can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. PedvaxHIB is not recommended for use in pregnant women.

ADVERSE REACTIONS: In early clinical studies involving the administration of 8,086 doses of PedvaxHIB alone to 5,027 healthy infants and children 2 months to 71 months of age, PedvaxHIB was generally well tolerated. No serious adverse reactions were reported. During a two-day period following vaccination with PedvaxHIB in a subset of these infants and children, the most frequently reported adverse reactions, excluding those shown in the first table, in decreasing order of frequency, included: irritability, sleepiness, respiratory infection/symptoms, and ear infection/otitis media. Urticaria was reported in two children. Thrombocytopenia was seen in one child. A cause-and-effect relationship between these side effects and the vaccination has not been established.

Selected objective observations reported by parents over a 48-hour period in infants and children 2 to 71 months of age following primary vaccination with PedvaxHIB alone are summarized in the first table.

In The Protective Efficacy Study, 4,459 healthy Navajo infants 6 to 12 weeks of age received PedvaxHIB or placebo. Most of these infants received DTP/OPV concomitantly. No differences were seen in the type and frequency of serious health problems expected in this Navajo population or in serious adverse experiences reported among those who received PedvaxHIB and those who received placebo, and none was reported to be related to PedvaxHIB. Only one serious reaction (tracheitis) was reported as possibly related to PedvaxHIB and only one (diarrhea) as possibly related to placebo. Seizures occurred infrequently in both groups (9 occurred in vaccine recipients, 8 of whom also received DTP; 8 occurred in placebo recipients, 7 of whom also received DTP) and were not reported to be related to PedvaxHIB. The frequencies of fever and local reactions occurring in a subset of these infants during a 48-hour period following each dose were similar to those seen in early clinical studies (see first table).

As with any vaccine, there is the possibility that broad use of PedvaxHIB could reveal adverse reactions not observed in clinical trials.

Potential Adverse Reactions: The use of Haemophilus b polysaccharide vaccines and another Haemophilus b conjugate vaccine has been associated with the following additional adverse effects: early onset of Haemophilus b disease and Guillain-Barré syndrome. A cause-and-effect relationship between these side effects and the vaccination was not established.

Fever or Local Reactions in Subjects 2 to 71 Months of Age Vaccinated with PedvaxHIB Alone: Other Clinical Studies

		Dose 1				Dose 2			
Age (Months)	Reaction	Number of Subjects Evaluated	6 hr.	24	48	Number of Subjects Evaluated	6 hr.	24	48
2-14*	Fever >38.3°C (101°F) Rectal	532	2.4%	3.8%	1.9%	329	3.0%	4.3%	3.6%
	Erythema >2.5 cm diameter	1,026	0.2%	1.0%	0.4%	585	0.9%	1.2%	0.7%
	Swelling/ Induration >2.5 cm diameter	1,026	0.6%	1.5%	1.6%	585	0.9%	2.8%	3.7%
15-71**	Fever >38.3°C (101°F) Rectal	149	4.0%	4.0%	6.7%				
	Erythema >2.5 cm diameter	572	0.0%	0.3%	0.2%				
	Swelling/ Induration >2.5 cm diameter	572	0.9%	2.1%	1.4%				

*Additional complaints reported following vaccination with the first and second dose of PedvaxHIB, respectively, in the indicated number of subjects were: nausea, vomiting, and/or diarrhea (101, 41), crying for more than one-half hour (43, 15), rash (16, 17), and unusual high-pitched crying (4, 4).

**Additional complaints reported following vaccination with one dose of PedvaxHIB in the indicated number of subjects were: nausea, vomiting, and/or diarrhea (44), crying for more than one-half hour (19), rash (12), and unusual high-pitched crying (0).

DOSAGE AND ADMINISTRATION:

FOR INTRAMUSCULAR ADMINISTRATION. DO NOT INJECT INTRAVENOUSLY.

2 to 14 Months of Age: Infants 2 to 14 months of age should receive a 0.5-mL dose of vaccine ideally beginning at 2 months of age followed by a 0.5-mL dose 2 months later (or as soon as possible thereafter). When the primary two-dose regimen is completed before 12 months of age, a booster dose is required (see text and second table).

15 Months of Age and Older: Children 15 months of age and older previously unvaccinated against Haemophilus b disease should receive a single 0.5-mL dose of vaccine.

Booster Dose: In infants completing the primary two-dose regimen before 12 months of age, a booster dose (0.5 mL) should be administered at 12 months of age but not earlier than 2 months after the second dose.

DATA ARE NOT AVAILABLE REGARDING THE INTERCHANGEABILITY OF OTHER HAEMOPHILUS b CONJUGATE VACCINES AND PedvaxHIB® (Haemophilus b Conjugate Vaccine [Meningococcal Protein Conjugate], MSD).

Vaccination Regimens by Age Group
(see text for details)

Age (Months) at First Dose	Primary	Age (Months) at Booster Dose
2-10	2 doses, 2 months apart	12
11-14	2 doses, 2 months apart	—
15-71	1 dose	—

TO RECONSTITUTE, USE ONLY THE ALUMINUM HYDROXIDE DILUENT SUPPLIED.

First, agitate the diluent vial; then, using sterile technique, withdraw the entire volume of aluminum hydroxide diluent into the syringe to be used for reconstitution. Inject all the aluminum hydroxide diluent in the syringe into the vial of lyophilized vaccine, and agitate to mix thoroughly.

Withdraw the entire contents into the syringe and inject the total volume of reconstituted vaccine (0.5 mL) intramuscularly, preferably into the anterolateral thigh or the outer aspect of the upper arm.

It is recommended that the vaccine be used as soon as possible after reconstitution. Store reconstituted vaccine in the vaccine vial at 2° to 8°C (36° to 46°F) and discard if not used within 24 hours. Agitate prior to injection.

Parenteral drug products should be inspected visually for extraneous particulate matter and discoloration prior to administration whenever solution and container permit. Aluminum hydroxide diluent and PedvaxHIB when reconstituted are slightly opaque white suspensions.

Special care should be taken to ensure that the injection does not enter a blood vessel.

It is important to use a separate sterile syringe and needle for each patient to prevent transmission of hepatitis B or other infectious agents from one person to another.

HOW SUPPLIED: No. 4792—PedvaxHIB is supplied as a single-dose vial of lyophilized vaccine, NDC 0006-4792-00, and a vial of aluminum hydroxide diluent.

No. 4797—PedvaxHIB is supplied as follows: a box of 5 single-dose vials of lyophilized vaccine, NDC 0006-4797-00, and 5 vials of aluminum hydroxide diluent.

Storage: Before reconstitution, store PedvaxHIB at 2° to 8°C (36° to 46°F). Store reconstituted vaccine in the vaccine vial at 2° to 8°C (36° to 46°F) and discard if not usec within 24 hours.

DO NOT FREEZE the aluminum hydroxide diluent or the reconstituted vaccine.

For more detailed information, consult your MSD Representative or see Prescribing Information.

Merck Sharp & Dohme, Division of Merck & Co., INC., West Point, PA 19486.

MSD
MERCK SHARP & DOHME

MAKING VACCINES THAT MAKE HISTORY

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Classified Advertising

All classified advertising orders, correspondence and payments should be directed to: American Journal of Diseases of Children, P.O. Box 1510, Clearwater, Florida 34617. Our telephone numbers are: 800-237-9851; 813-443-7666. Please do not send classified ads, payments or related correspondence to the AMA headquarters in Chicago. This causes needless delay.

Inquiries about "BOX NUMBER" advertisements: All replies must be in writing and must cite the box number in the ad. Example: Box ______, c/o AJDC, P.O. Box 1510, Clearwater, Florida 34617. We are not permitted to divulge the identity of advertisers who wish their mail sent in care of American Journal of Diseases of Children.

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P.O. Box 1510, Clearwater, Florida 34617

For assistance with your ad schedule call toll free:
800-237-9851 ☐ 813-443-7666

Professional Opportunities

PHILADELPHIA AREA: Three pediatricians seeking BE/BC fourth in growing suburban community. One office practice, minutes from hospital. Full partnership opportunity after two years. Convenient access to Philadelphia, recreational opportunities in nearby Pocono Mountains and/or New Jersey Beaches. Send CV to: Stephen R. Gershenson, MD, 87 Bethlehem Pike, Montgomeryville, PA 18936.

ALL PEDIATRIC SPECIALTIES — NATIONWIDE. Group/solo. Dr. Len Goodman, 5600 Executive Center Drive, #102, Charlotte, NC 28212. (704) 36-2527.

Professional Opportunities

OBERLIN, OHIO — Multi-specialty group seeks BC/BE pediatricians to serve growing patient load. Northern Ohio college town serving drawing area of 275,000. Salary, liberal benefits first year with full shareholder status available thereafter. Send CV to: Dr. VanDyke, 224 West Lorain, Oberlin, OH 44074.

COLORADO — BC/BE pediatrician to join seven-pediatrician department of established, multi-specialty clinic. Contact: Jos. L. Corrigan, MD, 209 South Nevada Avenue, Colorado Springs, CO 80903. (719) 475-7700.

— COLUMBUS, OHIO —

Neonatologist to join one other neonatologist in a newly opened labor and delivery/NICU. This modern hospital is located in a rapidly expanding suburb of Ohio's largest metropolitan area. This progressive city with its medical school and state university is an ideal place to satisfy both personal and professional needs. To learn more about this new, attractive opportunity we encourage you to call now while this opening still exists. Barbara Lakoski: 1-800-243-4353.

STRELCHECK & ASSOCIATES, INC.
12724 N. Maplecrest Lane
Mequon, WI 53092

NEWPORT, VERMONT: Board-certified, solo practitioner seeks BE/BC associate to join a rapidly growing solo practice, early partnership possible. Beautiful, rural, northern Vermont. Challenging patient load. Good university affiliations. Reply: T.A.E. Moseley, MD, North Country Hospital, Newport, VT 05855.

MAINE—Pediatric hematologist/oncologist to continue and expand well-established, hospital-based program. Affiliated with 400-bed tertiary center serving over 400,000. Joint clinical-academic medical school appointment. P.O.G. satellite in development. Attractive university community one hour from coast; two hours from Sugarloaf USA; one hour flight from Boston. Competitive salary and benefits. Send CV to: New England Health Search, 63 Forest Avenue, Orono, ME 04473. Or call: (207) 866-5680.

ENGLEWOOD/LITTLETON, COLORADO—A 320-bed, not-for-profit hospital in south suburb of Denver seeking pediatricians to join busy private practice. Expect to work hard, see 35-40 patients a day. Must be board-certified or -eligible, prefer university or hospital trained. Please send CV to: Swedish Medical Center, P.O. Box 2901, Englwood, CO 80150-0101. Attention: Physician Services.

TEXAS — BE/BC pediatrician to join busy, three-pediatrician group in Dallas/Fort Worth Metroplex. Competitive salary, incentives and benefits. Contact: Dan Geppert, MD, 950 North Davis, Arlington, TX 76012. (817) 460-0104.

THIRD PEDIATRICIAN with neonatology experience to join pediatric group in central New Jersey. 443-bed community teaching hospital. Assistance with start-up costs. Send CV to: Box #118, c/o AJDC.

THIRD PEDIATRICIAN—BRAINERD, MINNESOTA: Join two pediatricians of 22 multi-specialty clinic. No set-up cost. Two hours from Minneapolis. Beautiful lakes and trees; ideal for families. Call collect/write: Curt Nielsen, (218) 828-7105 or (218) 829-4901; Brainerd Medical Center, P.O. Box 524, Brainerd, MN 56401.

Professional Opportunities

BC/BE PEDIATRICIAN to join three pediatricians in university-run ambulatory center with regional hospital and university medical center affiliation, with emphasis on primary care. UMMC is an equal opportunity/affirmative action employer. Location: Southcentral Massachusetts. Appointment in university department of pediatrics. Membership in university group practice. Fringe benefits excellent. Salary negotiable. Reply: David P. Tapscott, MD, 281 East Hartford Avenue, Uxbridge, MA 01569-9658.

OHIO—Well established solo pediatrician seeks BC/BE associate in primary care oriented practice experiencing explosive growth. Salary guarantee with opportunity for partnership arrangement (full-time) or part-time option (negotiable). May begin any time. Attractive community with children's hospital and university/medical school affiliations. Send CV or contact: Cheryl Peters or John Ginger, MD, 3080 Ackerman Boulevard, Suite 110, Dayton, OH 45429. (513) 298-4120.

FOUR CONGENIAL PEDIATRICIANS seek fifth pediatrician for rapidly expanding practice. This practice is located in an affluent growing community in northern California within a two-hour access to San Francisco and Lake Tahoe. Guaranteed salary for two years with partnership options at the end of the two-year period. Write or call: P.O. Box 787, Lodi, CA 95240. (209) 369-7493.

COLORADO: Excellent private practice opportunity for two BE/BC pediatricians. Non-urban setting close to Denver. MRI/CT, 24-hour emergency and supportive medical staff. Reply: Physician Recruitment Committee, c/o L. York, McKee Medical Center, 2000 Boise, Loveland, CO 80538.

Regional medical center for 85,000 population needs pediatricians; located in beautiful mountainous eastern Kentucky with state parks and lakes within thirty miles. Progressive community with excellent accredited school system. Active staff, 60 practicing physicians. If interested, send CV to:

Dr. John Tummons, Administrator
Methodist Hospital of Kentucky
911 South Bypass, Pikeville, KY 41501

MANKATO, MINNESOTA—A large multi-specialty group practice is seeking a BC/BE physician to join its five-person pediatric department. Consider practicing in a "micropolitan area"—a smaller city with cosmopolitan qualities. Mankato is ranked ninth as one of the best small cities in the United States to live. First year salary guarantee plus incentive and excellent corporate benefits, along with shareholder status after twelve months For additional information, please call or send CV to: John Norris, MD, or Roger Greenwald, Executive Vice President, 501 Holly Lane, Mankato, MN 56001. (507) 625-1811.

MAINE: Immediate opportunity for a fourth BC/BE pediatrician with general and/or subspecialty interests to join a multi-specialty group affiliated with a 250-bed regional referral hospital. Enjoy the professional challenge offered in a sophisticated medical community along with the wonderful recreational opportunities and quality of life in Maine. Please send CV to: Richard Marsh, MD, 76 High Street, Suite 203, Lewiston, ME 04240. Or call: (207) 795-2389 and ask for Shannon Tamminen.

PLEASE NOTE—Address replies to box number ads as follows: Box number, ______, c/o AJDC, P.O. Box 1510, Clearwater, FL 34617.

TWO PEDIATRICIANS SEEKING third BC/BE pediatrician to join two site, growing practice. Ideal all season recreational area. Ideal site for young family. Please contact: Tahoe City Pediatrics, P.O. Box 6959, Tahoe City, CA 95730.

ROCHESTER, NEW YORK

Eleven member pediatric division of multi-specialty group practice serving prepaid and fee-for-service patients looking for twelfth pediatrician to do general pediatrics. In addition to full-time position, willing to consider part-time or job-share opportunities. Subspecialty interests possible. University affiliation encouraged. Competitive salary and benefits. Located in attractive metropolitan area with many cultural and recreational advantages.

Send resume or call:

ROCHESTER MEDICAL GROUP, P.C.
Attention: James Tobin, MD
800 Carter Street, Rochester, NY 14621
(716) 338-1400 • EOE, M/F

THE DEPARTMENT OF PEDIATRICS, William Beaumont Hospital, is seeking a second pediatric cardiologist to expand our Division of Pediatric Cardiology. William Beaumont Hospital is a 934-bed general hospital with 20 residency programs and a fully accredited training program in pediatrics. The Department of Pediatrics has 23 full-time, 12 part-time and a number of geographic full-time faculty. The inpatient service includes a 52-bed general pediatric ward, a 4-bed PICU (to increase to 6 beds by the summer) and a 30-bed NICU. We are anxious to recruit an individual who is interested in clinical care and teaching but who also has a definite interest in scholarly activity. Contact: M. Jeffrey Maisels, MD, Chairman, Department of Pediatrics, William Beaumont Hosital, 3601 West 13 Mile Road, Royal Oak, MI 48073-6769. (313) 551-0412.

PEDIATRICIAN

Immediate opportunity to associate with five pediatricians in a 70-doctor multi-specialty group. Drawing area of 400,000. Modern hospital within five minutes of clinic. Stimulating Big-10 university community of 110,000 with superb cultural advantages. Ideal for families. Medical school teaching affiliation if desired. Excellent initial guarantee and fringes with early associate status, subsequent income based exclusively on productivity. Send CV to:

RONALD H. DEERING, MD
Christie Clinic Association
101 West University
Champaign, IL 61820

Pediatric Subspecialists

Cardiology
Pulmonology
Hematology/Oncology
Neurology
Surgery
Neonatology

The University of South Dakota School of Medicine currently has openings for BE/BC pediatric subspecialties.

These are full-time academic positions ideally suited for the clinician scholar who wishes to develop and guide a program which will have a significant impact on the health care of children. Although our program is heavily slanted toward medical student education and patient care, the department encourages and provides ample resources for clinical and laboratory research.

Sioux Falls, included in David Frankes' book, America's Fifty Safest Cities, has a strong economic base, growing population and a progressive educational system. South Dakota's four season climate welcomes endless recreational activities year-round.

Competitive financial packages offered. EOE/AAE.

Send CV or call:
Carl Hinson • (800) 468-3333

USD School of Medicine
1100 South Euclid, P.O. Box 5039
Sioux Falls, SD 57117

PEDIATRICS

Immediate opening for qualified pediatrician in an established, large multi-specialty group in Western Kentucky. The opportunity offers:

- competitive salary and benefit package
- malpractice insurance
- partnership eligibility in two years
- no buy-in required
- teaching opportunities with university affiliation

The community offers:

- state-of-the-art medicine in semi-rural area
- family oriented community
- relaxed lifestyle not available in large cities
- metropolitan areas easily accessible
- large lakes nearby with excellent recreational opportunities

Interested parties send CV to:

Physician Recruitment
Trover Clinic
200 Clinic Drive
Madisonville, KY 42431
Phone: (502) 825-7470

ADOLESCENT MEDICINE

Unique opportunity for academic adolescent medicine specialist. The Department of Pediatrics, Northwestern University Medical School is seeking a Head of Adolescent Medicine for its patient care and educational programs at the Evanston Hospital and the Children's Memorial Hospital. This individual will spend the majority of time at The Evanston Hospital serving the needs of adolescents, including a Child and Adolescent Center with over 2,000 adolescent visits annually. Participation in the University Student Health Service is available.

This position will have responsibility for a teaching curriculum in adolescent medicine for 60+ pediatric residents from the Residency Training Program of Children's Memorial Hospital. Ample time will be provided for clinical research. Interest in sports medicine is desirable. Board-eligibility/-certification in pediatrics and completion of an adolescent medicine fellowship are required. Faculty rank and salary will be commensurate with a candidate's experience.

Interested candidates should send curriculum vitae and supporting documents to:

David Ingall, MD, Chairman
Department of Pediatrics

THE EVANSTON HOSPITAL
2650 Ridge Avenue, Evanston, IL 60201

The Evanston Hospital and Children's Memorial Hospital are affirmative action and equal opportunity employers.

Pediatrician

—North Carolina—

Sixteen miles from Greensboro, hospital supported solo practice sharing call with two other solo pediatricians.

Excellent compensation; assistance with start-up costs. Family oriented, low stress lifestyle with nearby metropolitan area, colleges, cultural activities, golf, easy drive to mountains or coast.

Call Carol Paule
for details at:

(800) 765-3055.

Professional Opportunities

SUFFOLK COUNTY NEW YORK — Seeking general pediatrician BE/BC part-time and vacation coverage to start, with possibility of full-time partnership. Call: (516) 589-6727.

PEDIATRICIAN

Combine private practice efficiency and compensation with the rewards of community-oriented practice. Enjoy working with a practitioner-centered management team. Nearly rural living twenty minutes from metropolitan area allows the perfect reconciliation between love of family and passion for medicine.

Guaranteed salary, excellent benefit package. Flexible working schedule. Computerized office. Stimulating patient mix, friendly area. Health education, social work and mid-level support. Excellent local hospital referral centers nearby. Medical school affiliation and faculty appointment possible. Exciting educational opportunities at local college. Affordable housing, excellent schools. Varied recreational opportunities.

We've got it all!

Send CV to: James Goetz, MD
Medical Director

Oak Orchard
Community Health Center
80 West Avenue, Brockport, NY 14420

CHIEF OF PEDIATRICS — North Shore Comprehensive Care, P.C. is a nine-member primary care group practice offering a full range of general medical services to residents of the historic and affluent North Shore of Massachusetts. This professional opportunity offers partnership in three years. On call responsibilities are shared with all pediatricians. North Shore Comprehensive Care, P.C. is affiliated with Beverly Hospital, a highly respected non-profit institution in the community. Our four branch offices are located on the seashore within 20 miles of Boston, close to surrounding recreational and cultural environments that are unsurpassed. This position is located in our Danvers office. If you are interested in this opportunity in our successful, expanding practice, please contact: Barbara Nadeau, Director of Human Resources, North Shore Comprehensive Care, P.C., 550 Cabot Street, Beverly, MA 01915. (508) 777-0980. An equal opportunity employer.

Position Available

PEDIATRICIANS NEEDED: BE/BC full-time, needed to join Carle Clinic — Danville, Illinois; a 40,000+ rural, industrial community on the scenic Illinois/Indiana border, draws patients from both states. This 15 physician group is part of a 210 physician, multi-specialty, group practice in central Illinois; liberal fringe benefits including liability coverage, and competitive salary leading to equal ownership. Write, including CV to: Robert C. Parker, Jr., MD, Assistant to the Chief Executive Officer, Carle Clinic Association, 602 West University, Urbana, IL 61801. Or call collect at (217) 337-3417, FAX (217) 337-3163.

PRESIDENT
AMERICAN BOARD OF PEDIATRICS

The American Board of Pediatrics has appointed a search committee to select a President of the Board with service to begin in 1991. The person selected for this full-time position will serve as the Chief Executive Officer of the Board.

We seek a distinguished, certified pediatrician who is an experienced educator and who is familiar with the procedures and operations of the American Board of Pediatrics.

Send nominations with a curriculum vitae to the Chairman of the Search Committee, Laurence Finberg, MD, at 111 Silver Cedar Court, Chapel Hill, NC 27514.

ILLINOIS

Position available for
board-certified/-eligible

PEDIATRICIAN

for existing practice with three other board-certified pediatricians (vacancy due to retiring physician). Our 33-physician, multi-specialty clinic is located 115 miles from Chicago, 50 miles from Rockford and is adjacent to a 135-bed, acute care hospital, with a Level II Nursery having state-of-the-art equipment.

Sterling is a "certified city" situated along the Rock River and with its twin city of Rock Falls, has a combined population of 30,000 people, and offers a fine living environment for family with stable economy, recreational opportunities and excellent schools—schools which have scored above the national average in ACT testing—and a park district which has twice received national recognition.

This positions offers an attractive call schedule of every fourth night and fourth weekend. Phone calls during the daytime are covered by well-trained RNs to free up time for clinical practicing pediatrics without interruption. Excellent first year guaranteed salary with incentives; partnership opportunity after one year.

Send CV to: E. Scott Bowmer, Administrator,

Sterling Rock Falls Clinic, Ltd.
101 E. Miller Road, Sterling, IL 61081

Directors Wanted

NEONATAL CO-DIRECTOR sought: BC/BE neonatologist for fee-for-service private practice in Level II, 18-bed nursery with 1,800 plus deliveries. Clinical, administrative and minimal teaching responsibilities (medical school and family practice residency). 150-bed, referral hospital located in Illinois university city. Great educational and recreational opportunities. Call Georgetta: (800) 328-3666.

Faculty Positions

AMBULATORY PEDIATRICS—Nonspecified: The Department of Pediatrics, University of Illinois College of Medicine at Rockford seeks a BC/BE pediatrician for an academic position in an ambulatory setting. The Community Health Center program is a longitudinal, comprehensive experience in primary care medicine. Each center is staffed by full-time faculty. Responsibilities include supervision of medical students in an ambulatory setting, direct patient care, quality assurance activities and clinical research. For earliest consideration please reply by: May 1, 1991. Reply with CV to: D.H. Wortmann, MD, Chairman, Department of Pediatrics, UICOM-R, 1400 Charles Street, Rockford, IL 61104. UICOM-R is an equal opportunity/affirmative action employer.

SOUTHEAST USA—academic pediatrician: Teach medical students and family practice residents. Direct patient care and clinical research interests required. Alabama state medical license required. Should be board-eligible or board-certified. The University of Alabama is an equal opportunity affirmative action employer. Send inquiries with CV to: David C. Hefelfinger, MD, Department of Pediatrics, 700 University Boulevard East, Tuscaloosa, AL 35401. (205) 348-1304.

PLEASE NOTE—Address replies to box number ads as follows: Box number, ______, c/o AJDC, P.O. Box 1510, Clearwater, FL 34617.

Faculty Positions

PEDIATRIC HEMATOLOGIST/ONCOLOGIST — Loyola University of Chicago, Stritch School of Medicine, Department of Pediatrics, is recruiting an Assistant Professor for the Section of Hematology/Oncology. Applicant must be sub-board certified or eligible, with expertise in hematology/oncology research. Interested applicants are invited to send their CV to: Carlos R. Suarez, MD, Director, Section of Pediatric Hematology/Oncology, 2160 South First Avenue, Maywood, IL 60153. Loyola University of Chicago is an equal opportunity educator and employer. Qualified persons are not subject to discrimination on the basis of a handicap.

CHIEF OF PEDIATRICS

Englewood Hospital, a 547-bed community hospital, with a major teaching affilation with the Mount Sinai School of Medicine, is seeking a qualified individual for the position of Chief of Pediatrics. Applicants must be accomplished academic physicians with administrative experience and excellent interpersonal skills; and be able to qualify for a faculty appointment at the Mount Sinai School of Medicine as associate professor or professor of pediatrics. Send CV to:

Alexander Hyatt, MD, Chairman
Chief of Pediatrics Search Committee
President's Office
ENGLEWOOD HOSPITAL
350 Engle Street, Englewood, NJ 07631

PEDIATRICIAN/NEONATOLOGIST—Board-eligible/-certified pediatrician or neonatologist for a position in a ten person multi-specialty pediatric department at 175-bed (2,000 deliveries per year), state owned hospital. Responsibilities include primary patient care and teaching of medical students and house officers. All applicants must have skills in resuscitation and stabilization of critically ill children, infants, new borns. Individuals with pediatric subspecialty are of special interest. For further information, please send CV or letter of interest to: Richard F. Howes, MD, University Medical Center, 2390 West Congress Street, Lafayette, LA 70506.

OPPORTUNITY IN FLORIDA — The University of South Florida College of Medicine, Department of Pediatrics, is seeking a Speech Pathologist/Therapist with PhD degree for appointment at Instructor level with the Section of Child Development. The University of South Florida College of Medicine is one of the truly developing medical schools in the Southeastern United States. The college is affiliated with nine hospitals and operates from campuses in the Tampa/St. Petersburg area which offers an environment and lifestyle that cannot be matched. Salary negotiable. Send letter of interest and resume to: Herbert H. Pomerance, MD, Professor and Interim Chairman, University of South Florida College of Medicine, Department of Pediatrics, 12901 Bruce B. Downs Boulevard, MDC Box 15, Tampa, FL 33612. (813) 974-4214. EOE. Federal law requires proper documentation of indentity and employability at the time of employment.

OPPORTUNITY FOR AN academically oriented clinician in the allergy program at Children's Hospital of Philadelphia with a faculty appointment at the University of Pennsylvania School of Medicine. The University of Pennsylvania is an equal opportunity/affirmative action employer. Reply to: Dr. David Cornfeld, Deputy Physician-in-Chief, Children's Hospital of Philadelphia, 34th and Civic Center Boulevard, Philadelphia, PA 19104 with CV and three references.

PEDIATRIC CARDIOLOGY — Assistant/Associate Professor: The Department of Pediatrics, Univesity of Illinois College of Medicine at Rockford seeks candidates for academically based full-time Associate Director for Division of Pediatric Cardiology. Position includes commitment to high quality of patient care, medical student/house staff teaching, and protected time for research. Must be BC/BE and eligible for licensure in Illinois. For earliest consideration please reply by May 1, 1991. Reply with CV to: D.H. Wortmann, MD, Chairman, Department of Pediatrics, UICOM-R, 1400 Charles Street. Rockford, IL 61104. UICOM-R is a equal opportunity/affirmative action employer.

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DEPARTMENT OF PEDIATRICS AND ADOLESCENT MEDICINE

Nominations and applications are invited for the chair of the Department of Pediatrics and Adolescent Medicine, St. Louis University School of Medicine. The department provides a full range of clinical services in pediatrics at the Cardinal Glennon Children's Hospital. The 190 bed hospital is located adjacent to the School of Medicine and the St. Louis University Hospital. The department is responsible for teaching medical students, training residents and fellows, and carrying on a productive program of research. The hospital in conjunction with the School of Medicine has established the Pediatric Research Institute to further the research endeavors of the department.

Nominations and applications should be addressed to David Lagunoff, M.D., Chairman of the Search Committee, 301 Caroline, St. Louis University School of Medicine, 1402 South Grand Boulevard, St. Louis, MO 63104. (314) 577-8108

St. Louis University Medical Center

Cardinal Glennon Children's Hospital

An affirmative action/ equal opportunity employer M/W/H

Locum Tenens

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M. R. Chacko, G. S. Parcel

Improving the Use of Early Follow-up Care After Emergency Department Visits: A Randomized Trial

E. W. Nelson, S. Van Cleve, M. K. Swartz, W. Kessen, P. L. McCarthy

Influenza Vaccination in the Prevention of Acute Otitis Media in Children

T. Heikkinen, O. Ruuskanen, M. Waris, T. Ziegler, M. Arola, P. Halonen

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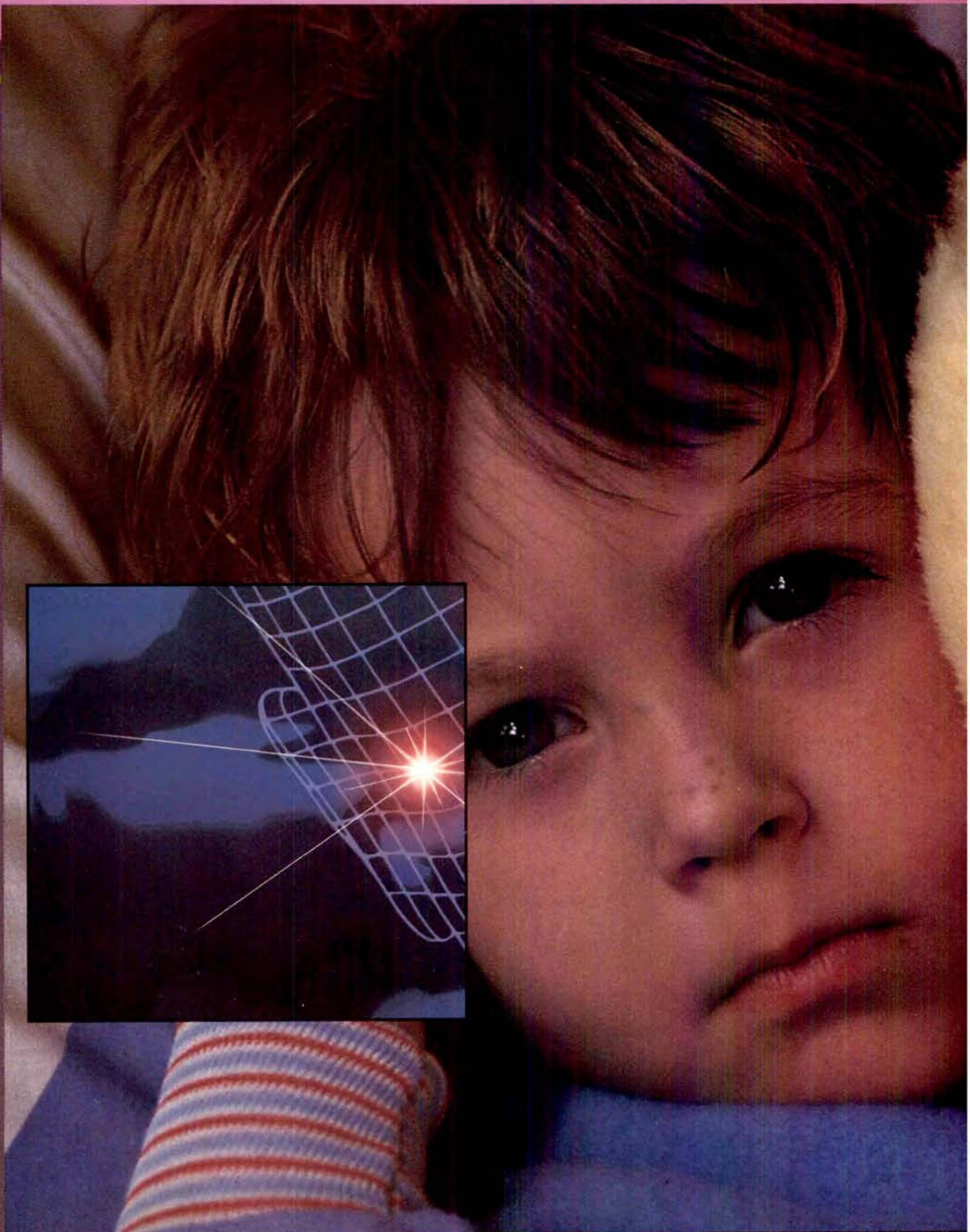

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AMERICAN JOURNAL OF DISEASES OF CHILDREN

AJDC

Vol 145 **No. 4** **APRIL 1991**

AMBULATORY PEDIATRIC ASSOCIATION:

PROGRAM AND ABSTRACTS 365

Annual Meeting of the Ambulatory Pediatric Association 383

THE PEDIATRIC FORUM

1991 Annual Meeting 425

Diphtheria and Tetanus Toxoids and Pertussis Vaccine Litigation 425
Howard Lokietz, MD, Arcadia, Calif

In Reply 425
Vincent A. Fulginiti, MD, New Orleans, La

Antibody Response to MMR Vaccination in Children Who Received IVIG as Neonates 425
Jeanne W. Ruderman, MD, Los Angeles, Calif;
Noori Barka, PhD,
James B. Peter, MD, PhD, Santa Monica, Calif;
E. Richard Stiehm, MD, Los Angeles, Calif

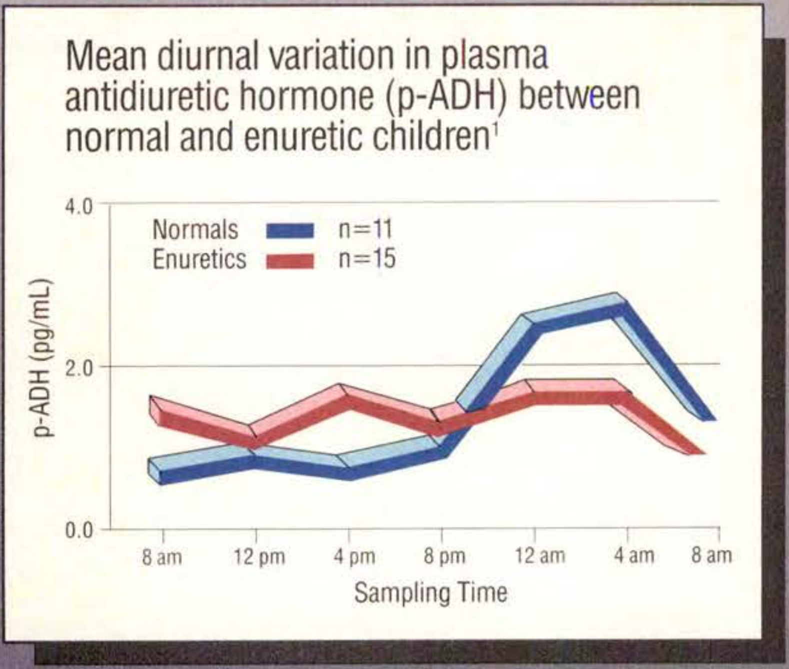
Vaccine Myth and Physician Handouts 426
Thomas P. Lynch, MD, Darien, Ill

In Reply 426
James D. Cherry, MD, Los Angeles, Calif

In Reply 427
Vincent A. Fulginiti, MD, New Orleans, La

Continued on page 355.

Landmark study concludes: Enuretic children may lack diurnal rhythm of ADH common in non-enuretic children[1]


Mean diurnal variation in plasma antidiuretic hormone (p-ADH) between normal and enuretic children[1]

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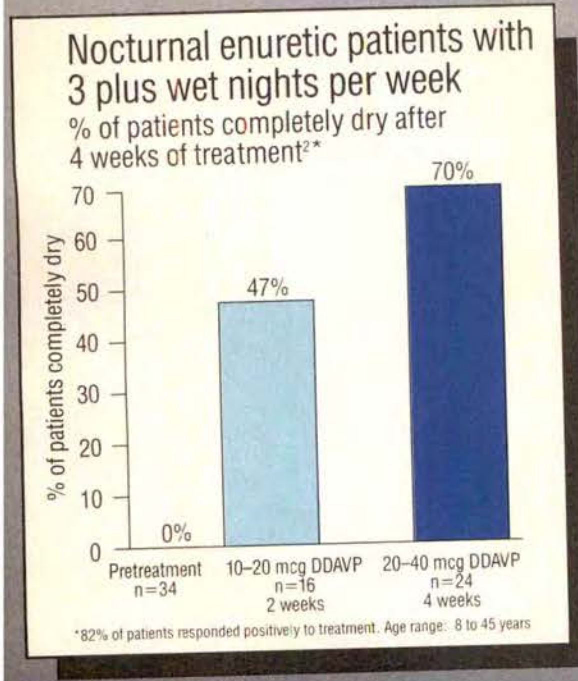
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% of patients completely dry after 4 weeks of treatment[2]*

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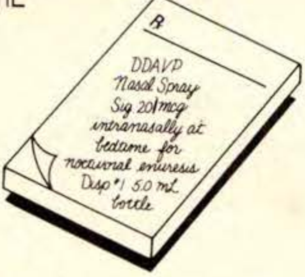

CONTRAINDICATION: Known hypersensitivity to DDAVP

WARNINGS: 1. For intranasal use only. 2. In very young and elderly patients in particular, fluid intake should be adjusted in order to decrease the potential occurrence of water intoxication and hyponatremia.

PRECAUTIONS:

General: DDAVP at high dosage has infrequently produced a slight elevation of blood pressure, which disappeared with a reduction in dosage. The drug should be used with caution in patients with coronary artery insufficiency and/or hypertensive cardiovascular disease because of possible rise in blood pressure.

Primary Nocturnal Enuresis: If changes in the nasal mucosa have occurred, unreliable absorption may result. DDAVP intranasal solution should be discontinued until the nasal problems resolve.

Information for Patients: Patients should be informed that the bottle accurately delivers 50 doses of 10 mcg each. Any solution remaining after 50 doses should be discarded since the amount delivered thereafter may be substantially less than 10 mcg of drug. No attempt should be made to transfer remaining solution to another bottle. Patients should be instructed to read accompanying directions on use of the spray pump carefully before use.

Laboratory Tests: For the healthy patient with primary nocturnal enuresis, serum electrolytes should be checked at least once if therapy is continued beyond 7 days.

DRUG INTERACTIONS: Although the pressor activity of DDAVP is very low compared to the antidiuretic activity, use of large doses of DDAVP with other pressor agents should only be done with careful patient monitoring.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY: Teratology studies in rats have shown no abnormalities. No further information is available.

PREGNANCY—CATEGORY B: Reproduction studies performed in rats and rabbits with doses up to 12.5 times the human intranasal dose (i.e. about 125 times the total adult human dose given systemically) have revealed no evidence of harm to the fetus due to desmopressin acetate. There are several publications of management of diabetes insipidus in pregnant women with no harm to the fetus reported; however, no controlled studies in pregnant women have been carried out. Published reports stress that, as opposed to preparations containing the natural hormones, DDAVP (desmopressin acetate) in antidiuretic doses has no uterotonic action, but the physician will have to weigh possible therapeutic advantages against possible dangers in each individual case.

NURSING MOTHERS: There have been no controlled studies in nursing mothers. A single study in a postpartum woman demonstrated a marked change in plasma, but little if any change in assayable DDAVP in breast milk following an intranasal dose of 10 mcg.

PEDIATRIC USE: Primary Nocturnal Enuresis: DDAVP has been used in childhood nocturnal enuresis. Short-term (4-8 weeks) DDAVP administration has been shown to be safe and modestly effective in children aged 6 years or older with severe childhood nocturnal enuresis. Adequately controlled studies with intranasal DDAVP in primary nocturnal enuresis have not been conducted beyond 4-8 weeks. The dose should be individually adjusted to achieve the best results.

There are reports of an occasional change in response with time, usually greater than 6 months. Some patients may show a decreased responsiveness, others a shortened duration of effect. There is no evidence this effect is due to the development of binding antibodies but may be due to a local inactivation of the peptide.

ADVERSE REACTIONS: Infrequently, high dosages have produced transient headache and nausea. Nasal congestion, rhinitis and flushing have also been reported occasionally along with mild abdominal cramps. These symptoms disappeared with reduction in dosage. Nosebleed, sore throat, cough and upper respiratory infections have also been reported.

The following table lists the percent of patients having adverse experiences without regard to relationship to study drug from the pooled pivotal study data for nocturnal enuresis.

ADVERSE REACTION	**PLACEBO (N=59)** %	**DDAVP 20 mcg (N=60)** %	**DDAVP 40 mcg (N=61)** %
BODY AS A WHOLE			
Abdominal Pain	0	2	2
Asthenia	0	0	2
Chills	0	0	2
Headache	0	2	5
Throat Pain	2	0	0
NERVOUS SYSTEM			
Depression	2	0	0
Dizziness	0	0	3
RESPIRATORY SYSTEM			
Epistaxis	2	3	0
Nostril Pain	0	2	0
Respiratory Infection	2	0	0
Rhinitis	2	8	3
CARDIOVASCULAR SYSTEM			
Vasodilation	2	0	0
DIGESTIVE SYSTEM			
Gastrointestinal Disorder	0	2	0
Nausea	0	0	2
SKIN & APPENDAGES			
Leg Rash	2	0	0
Rash	2	0	0
SPECIAL SENSES			
Conjunctivitis	0	2	0
Edema Eyes	0	2	0
Lachrymation Disorder	0	0	2

OVERDOSAGE: See adverse reactions above. In case of overdosage, the dose should be reduced, frequency of administration decreased, or the drug withdrawn according to the severity of the condition. There is no known specific antidote for DDAVP.

An oral LD_{50} has not been established. An intravenous dose of 2 mg/kg in mice demonstrated no effect.

HOW SUPPLIED: A 5 mL bottle with spray pump delivering 50 doses of 10 mcg (NDC 0075-2450-02). Keep refrigerated at 36°-46°F (2°-8°C). When traveling, product will maintain stability for up to 3 weeks when stored at room temperature, 72°F (22°C).

See product circular for full prescribing information. Rev. 6/89

1. Rittig S, Knudsen UB, Nørgaard JP, et al: Abnormal diurnal rhythm of plasma vasopressin and urinary output in patients with enuresis. *Am J Physiol* 1989;25(4):F664-F671. 2. Rittig S, Knudsen UB, Sørensen S, et al: Long-term double-blind cross-over study of desmopressin intranasal spray in the management of nocturnal enuresis. In: Meadow SR, ed. *Desmopressin in Nocturnal Enuresis: Proceedings of an International Symposium.* England: Horus Medical Publications; 1988:43-55. 3. Dimson SB: DDAVP and urine osmolality in refractory enuresis. *Arch Dis Child* 1986;61:1104-1107. 4. Data on file, Rhône-Poulenc Rorer Pharmaceuticals Inc. 5. Richardson DW, Robinson AG: Diagnosis and treatment: Drugs five years later: Desmopressin. *Ann Intern Med* 1985;103:228-239.

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INDEX TO ADVERTISERS

Burroughs Wellcome Company 428A-B

Carnation Company 356-357

Fisons Corporation 361-362

ICN Pharmaceuticals, Inc 448A-D

McNeil Consumer Products Company 364C-D, 355-356
Mead Johnson Nutritional Division 430
Merck Sharp & Dohme
Division of Merck & Co., Inc. 363-364

Partnership For A Drug-Free America 468

Rorer Pharmaceuticals 352-354

SmithKline-Beecham Laboratories .... Cover 2-350

Wyeth-Ayerst Laboratories .... 359-360, 453-454, 469-470, 475-476, Cover 4

While every precaution is taken to ensure accuracy, we cannot guarantee against the possibility of an occasional change or omission in the preparation of this index.

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AMP

AMERICAN JOURNAL OF DISEASES OF CHILDREN

Exhibitor 'Giveaways': A Curmudgeon's View 427
Lawrence R. Berger, MD, MPH, Albuquerque, NM

New York State Health Code 405 Update 428
Gerald E. Daigler, MD;
Robert C. Welliver, MD;
F. Bruder Stapleton, MD, Buffalo, NY

THE EDITORIAL BOARD SPEAKS

Complex Problem: Complex Solutions 429
Elizabeth McAnarney, MD, Rochester, NY

ARTICLES

Acquired Immunodeficiency Syndrome and Adolescents: Knowledge, Attitudes, and Behaviors of Runaway and Homeless Youths 431
Susan Tucker Sugerman, MD, MPH;
Albert C. Hergenroeder, MD;
Mariam R. Chacko, MD;
Guy S. Parcel, PhD, Houston, Tex

The Total Iron-Binding Capacity in Iron Poisoning: Is It Useful? 437
Milton Tenenbein, MD, FRCPC, FAAP,
Randall W. Yatscoff, PhD, FCACB, Winnipeg, Manitoba

Improving the Use of Early Follow-up Care After Emergency Department Visits: A Randomized Trial 440
Eliot W. Nelson, MD; Susan Van Cleve, RN, MSN, PNP;
Martha K. Swartz, RN, MSN, PNP; William Kessen, PhD;
Paul L. McCarthy, MD, New Haven, Conn

Influenza Vaccination in the Prevention of Acute Otitis Media in Children 445
Terho Heikkinen, MD; Olli Ruuskanen, MD;
Matti Waris, MSc; Thedi Ziegler, PhD; Mikko Arola, MD;
Pekka Halonen, MD, Turku, Finland

Mineral Metabolism and Calcitriol Therapy in Idiopathic Juvenile Osteoporosis 457
Giuseppe Saggese, MD; Silvano Bertelloni, MD;
Giampiero I. Baroncelli, MD;
Giuseppe Perri, MD; Andrea Calderazzi, MD, Pisa, Italy

Continued on page 358.

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Evaluation of Bayesian Forecasting for Individualized Gentamicin Dosage in Infants Weighing 1000 g or Less 463
Kei Lui, MBBS, FRACP;
Scott M. Bryson, MScPharm;
Danica B. Irwin, BScPharm;
Simon Costello, MBBS, FRACP, Toronto, Ontario

EDUCATIONAL INTERVENTION

The Pediatric Program Director: An Analysis of the Role and Its Problems 449
Jeffrey C. Weiss, MD, Philadelphia, Pa;
Robert A. Doughty MD, Wilmington, Del;
Richard Lampe, MD, Washington, DC

SPECIAL FEATURES

Radiological Case of the Month 471
Janice W. Allison, MD;
Carol A. Stephenson, MD;
Teresita L. Angtuaco, MD;
Charles M. Glasier, MD, Little Rock, Ark;
Beverly P. Wood, MD, Los Angeles, Calif

Picture of the Month 473
Zvi Laron, MD;
Beatrice Klinger, MD;
Michael Grunebaum, MD, Tel Aviv, Israel;
Murray Feingold, MD;
Walter P. Tunnessen, MD, Brighton, Mass

BOOK REVIEW

Current Concepts in Childhood Spinal Muscular Atrophy 462
Peggy C. Ferry, MD, Tucson, Ariz

REGULAR DEPARTMENTS

Index to Advertisers 354

Instructions for Authors 424

Classified Advertising 477

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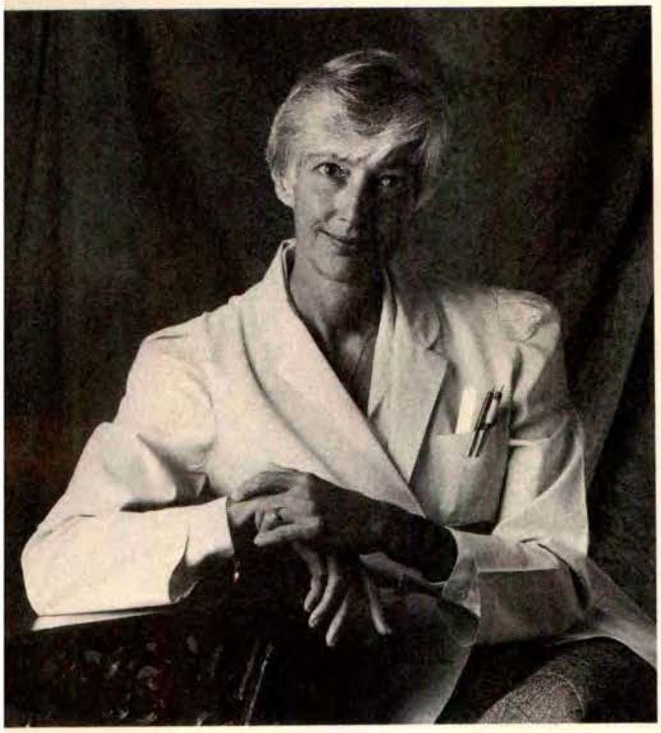

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WARNINGS: Risk of GI Ulcerations, Bleeding, and Perforation with NSAID Therapy: Physicians should remain alert for ulceration and bleeding in patients treated chronically with NSAIDS even in the absence of previous GI tract symptoms. In patients observed in clinical trials of several months' to two years' duration, symptomatic upper GI ulcers, gross bleeding or perforation appear to occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for one year.

Except for a prior history of serious GI events and other risk factors known to be associated with peptic ulcer disease, no risk factors have been associated with increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less well than other individuals and most spontaneous reports of fatal GI events are in this population.

PRECAUTIONS: General: Because serious GI tract ulceration and bleeding can occur without warning symptoms, physicians should follow chronically treated patients for the signs and symptoms of ulceration and bleeding.

Blurred and/or diminished vision, scotomata, and/or changes in color vision have been reported. If a patient develops such complaints the drug should be discontinued and the patient should have an ophthalmologic examination.

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Ibuprofen can inhibit platelet aggregation and prolong bleeding time. CHILDREN'S ADVIL® SUSPENSION should be used with caution in persons with intrinsic coagulation defects and those on anticoagulant therapy.

The antipyretic and anti-inflammatory activity of ibuprofen may reduce fever and inflammation, thus diminishing their utility as diagnostic signs in detecting complications of presumed noninfectious, noninflammatory painful conditions.

Small decreases (usually not exceeding one gram) in hemoglobin and hematocrit with an apparent dose response relationship have been observed following chronic administration. If there are no signs of bleeding, it is probably not clinically important.

To avoid exacerbation of disease or adrenal insufficiency, patients on prolonged corticosteroid therapy should have their therapy tapered slowly when CHILDREN'S ADVIL® SUSPENSION is added to the treatment program.

Aseptic meningitis: Aseptic meningitis with fever and coma has been observed on rare occasions in adult patients on ibuprofen therapy. Although it is more likely to occur in patients with systemic lupus erythematosus and related connective tissue diseases, it has been reported in adult patients who do not have underlying chronic disease. If signs or symptoms of meningitis develop in a patient on CHILDREN'S ADVIL® SUSPENSION, the possibility of its being related to ibuprofen should be considered.

Renal Effects: As with other nonsteroidal anti-inflammatory drugs, long-term administration of ibuprofen to animals has resulted in renal papillary necrosis and other abnormal renal pathology. In humans, there have been reports of acute interstitial nephritis with hematuria, proteinuria, and occasionally nephrotic syndrome.

A second form of renal toxicity has been seen in patients with prerenal conditions leading to reduction in renal blood flow or blood volume. In these patients, administration of a nonsteroidal anti-inflammatory drug may cause a dose dependent reduction in prostaglandin formation and precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, and those taking diuretics and the elderly. Those patients at high risk who chronically take CHILDREN'S ADVIL® SUSPENSION should have renal function monitored if they have signs or symptoms of azotemia. Discontinuation of nonsteroidal anti-inflammatory drug therapy is typically followed by recovery to the pretreatment state.

Since ibuprofen is eliminated primarily by the kidneys, patients with significantly impaired renal function should be closely monitored and a reduction in dosage should be anticipated to avoid drug accumulation.

Information for Patients: Physicians may wish to discuss with their patients the potential risks and likely benefits of treatment with CHILDREN'S ADVIL® SUSPENSION.

Laboratory Tests: Meaningful (3 times the upper limit of normal) elevations of SGPT or SGOT (AST) occurred in controlled clinical trials in less than 1% of patients. A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of more severe hepatic reactions while on therapy with ibuprofen. If abnormal liver tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur, CHILDREN'S ADVIL® SUSPENSION should be discontinued.

Diabetes: Each 5 mL of CHILDREN'S ADVIL® SUSPENSION contains 2.5 g of sucrose which should be taken into consideration when treating patients with impaired glucose tolerance. It also contains 350 mg of sorbitol per 5 mL. Although in clinical trials CHILDREN'S ADVIL® SUSPENSION was not associated with more diarrhea than control treatments, should a patient develop diarrhea, the physician may wish to review the patient's dietary intake of sorbitol from other sources.

Drug Interactions: *Coumarin-type Anticoagulants:* Bleeding has been reported when ibuprofen and other nonsteroidal anti-inflammatory agents have been administered to patients on coumarin-type anticoagulants; the physician should be cautious when administering CHILDREN'S ADVIL® SUSPENSION to patients on anticoagulants.

Aspirin: Concurrent use of aspirin is not recommended.

Methotrexate: In vitro studies indicate that ibuprofen could enhance the toxicity of methotrexate. Caution should be used if CHILDREN'S ADVIL® SUSPENSION is administered concomitantly with methotrexate.

H_2 Antagonists: In studies with human volunteers, coadministration of cimetidine or ranitidine with ibuprofen had no substantive effect on ibuprofen serum concentrations.

Furosemide: Ibuprofen can reduce the natriuretic effect of furosemide and thiazides in some patients. During concomitant therapy with CHILDREN'S ADVIL® SUSPENSION, the patient should be observed closely for signs of renal failure as well as to assure diuretic efficacy.

Lithium: Ibuprofen produced an elevation of plasma lithium levels (15%) and a reduction in renal lithium clearance (19%) in a study of 11 normal volunteers during the period of concomitant drug administration. Patients should be observed carefully for signs of lithium toxicity. Read package insert for lithium before its use.

Pregnancy: Administration of ibuprofen is not recommended during pregnancy or for use by nursing mothers.

Infants: Safety and efficacy of CHILDREN'S ADVIL® SUSPENSION in children below the age of 12 months have not been established.

ADVERSE REACTIONS: The most frequent type of adverse reaction occurring with CHILDREN'S ADVIL® SUSPENSION is gastrointestinal. In clinical trials among adults involving chronic administration of ibuprofen, the percentage of patients reporting one or more gastrointestinal complaints ranged from 4% to 16%.

Incidence Greater Than 1% (but less than 3%), Probable Causal Relationship (see PRECAUTIONS): Abdominal cramps or pain, abdominal distress, constipation, diarrhea, epigastric pain,* fullness of the GI tract (bloating and flatulence), heartburn,* indigestion, nausea,* nausea and vomiting; dizziness,* headache, nervousness; pruritus, rash* (including maculopapular type); tinnitus; decreased appetite; edema, fluid retention (generally responds promptly to drug discontinuation).

Precise Incidence Unknown (but less than 1%), Probable Causal Relationship (see PRECAUTIONS): Abnormal liver function tests, gastric or duodenal ulcer with bleeding and/or perforation, gastritis, gastrointestinal hemorrhage, hepatitis, jaundice, melena, pancreatitis; alopecia, erythema multiforme, Stevens-Johnson syndrome, urticaria, vesiculobullous eruptions; aseptic meningitis with fever and coma, confusion, depression, emotional lability, insomnia, somnolence; amblyopia (blurred and/or diminished vision, scotomata and/or changes in color vision), hearing loss; agranulocytosis, aplastic anemia, decreases in hemoglobin and hematocrit, eosinophilia, hemolytic anemia (sometimes Coombs' positive), neutropenia, thrombocytopenia with or without purpura; congestive heart failure in patients with marginal cardiac function, elevated blood pressure, palpitations; anaphylaxis, bronchospasm (see CONTRAINDICATIONS), syndrome of abdominal pain, fever, chills, nausea and vomiting; acute renal failure in patients with pre-existing significantly impaired renal function, azotemia, cystitis, decreased creatinine clearance, hematuria, polyuria; dry eyes and mouth, gingival ulcers, rhinitis.

Precise Incidence Unknown (but less than 1%), Causal Relationship Unknown: Dream abnormalities, hallucinations, paresthesias, pseudotumor cerebri; photoallergic skin reactions, toxic epidermal necrolysis; cataracts, conjunctivitis, diplopia, optic neuritis; bleeding episodes (e.g., epistaxis, menorrhagia); acidosis, gynecomastia, hypoglycemic reactions; arrhythmias (sinus tachycardia, sinus bradycardia); angioedema, Henoch-Schönlein vasculitis, lupus erythematosus syndrome, serum sickness; renal papillary necrosis.

*Reactions occurring in 3% to 9% of adult patients treated with ibuprofen.

OVERDOSAGE: Patients with a history of ingestion of greater than 100 mg/kg should have induced emesis or gastric lavage. Multiple dose oral administration of activated charcoal may be useful. Supportive therapy may include oxygen, respiratory support, and parenteral fluids. Because the drug is acidic and excreted in the urine, administration of sodium bicarbonate and induction of diuresis may be beneficial.

DOSAGE AND ADMINISTRATION: Fever: 5 mg/kg if baseline temperature is 102.5°F or below or 10 mg/kg if baseline temperature is greater than 102.5°F, every 6-8 hours (children); 400 mg every 4-6 hours (adults).

Mild to moderate pain in adults: 400 mg every 4 to 6 hours.

Juvenile Arthritis: 30-40 mg/kg day in 3 or 4 divided doses.

RA and OA: 1200-3200 mg per day in 3 or 4 divided doses.

Dysmenorrhea: 400 mg every 4 hours.

HOW SUPPLIED: 4 and 16 oz. bottles

Caution: Federal law prohibits dispensing without prescription.

References:

1. Walson PD, Galletta G, Braden NJ, Alexander L. Ibuprofen, acetaminophen, and placebo treatment of febrile children. *Clin Pharmacol Ther.* 1989;46:9-17.
2. Independent Clinical Study: Reduction of Fever in Children, Multiple Dose. Data on file, Medical Department, Whitehall Laboratories.
3. Independent Clinical Study: Reduction of Fever in Children, Single Dose. Data on file, Medical Department, Whitehall Laboratories.

WYETH™
PEDIATRICS

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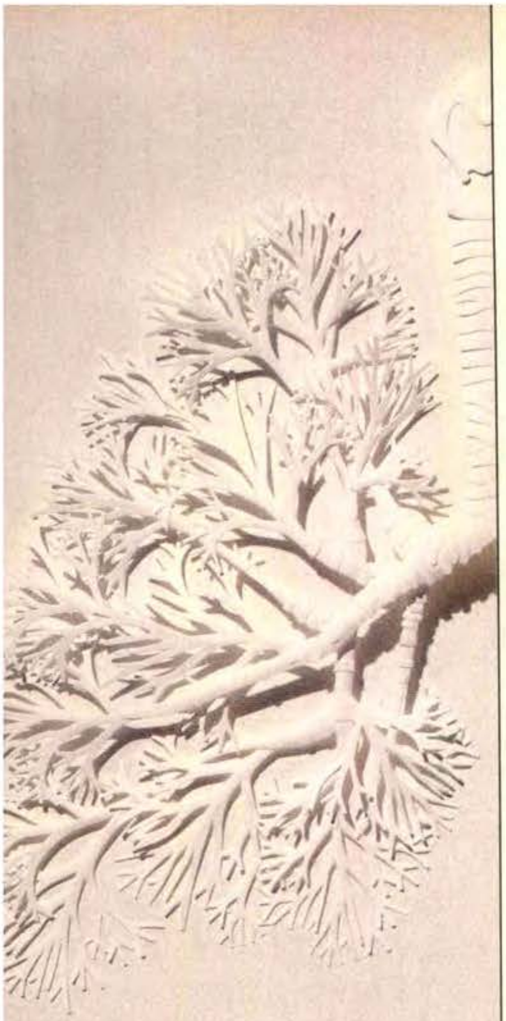
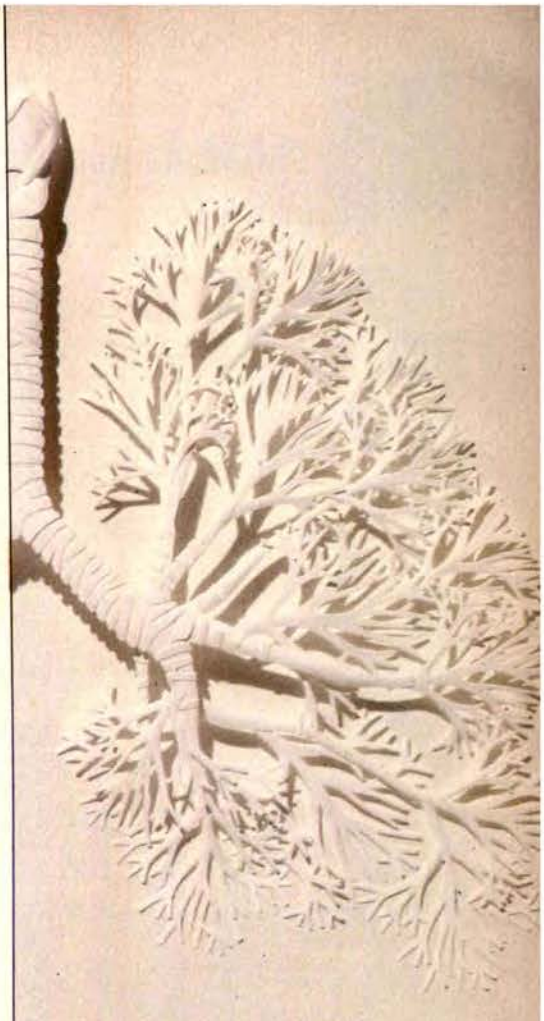


TWO SIDES OF ASTHMA THERAPY

FOUNDATION THERAPY
SYMPTOMATIC THERAPY



Asthma is more than just a series of symptomatic episodes. In fact, asthma is a four-part cycle... starting with the early response of bronchospasm, followed by bronchial inflammation, a late response, and bronchial hyperreactivity (which increases the likelihood of another episode). *Only INTAL® acts on all four of these processes.*

Prescribed as foundation therapy, INTAL improves pulmonary function and reduces asthma severity over time,[1] while providing safety in both children and adults.

FOUNDATION

INTAL®

(cromolyn sodium /FISONS)

COMPLEMENTS SYMPTOMATIC THERAPY

Symptomatic therapy—bronchodilators—acts only against the early response of bronchospasm. By combining symptomatic and foundation therapy, the four-part cycle of asthma is broken, and patients receive both immediate relief and long-term improvement.

INTAL is available in three convenient dosage forms, to meet the variety of patients' needs.

Prescribe INTAL in addition to symptomatic therapy...and see how effectively one complements the other.

FISONS
Pharmaceuticals
Rochester, NY 14623

See adjacent page for brief summary of Full Prescribing Information.

INTAL® Inhaler

(cromolyn sodium/FISONS)
800 mcg/Puff

DESCRIPTION: INTAL Inhaler (cromolyn sodium inhalation aerosol) is a metered dose aerosol unit for oral inhalation containing micronized cromolyn sodium, sorbitan trioleate with dichlorotetrafluoroethane and dichlorodifluoromethane as propellants. Each metered spray delivers to the patient approximately 800 mcg of cromolyn sodium. Each 8.1g canister delivers at least 112 metered sprays (56 doses); each 14.2g canister delivers at least 200 metered sprays (100 doses).

INDICATIONS AND USAGE: INTAL Inhaler is a prophylactic agent indicated in the management of patients with bronchial asthma.

CONTRAINDICATIONS: INTAL Inhaler is contraindicated in those patients who have shown hypersensitivity to cromolyn sodium or other components.

WARNINGS: INTAL Inhaler has no role in the treatment of an acute attack of asthma, especially status asthmaticus. Severe anaphylactic reactions can occur after cromolyn sodium administration. The recommended dosage should be decreased in patients with decreased renal or hepatic function. INTAL Inhaler should be discontinued if the patient develops eosinophilic pneumonia (or pulmonary infiltrates with eosinophilia). Because of the propellants in this preparation, it should be used with caution in patients with coronary artery disease or a history of cardiac arrhythmias.

PRECAUTIONS: General: In view of the biliary and renal routes of excretion for cromolyn sodium, consideration should be given to decreasing the dosage or discontinuing the administration of the drug in patients with impaired renal or hepatic function.

Occasionally, patients may experience cough and/or bronchospasm following cromolyn sodium inhalation. At times, patients who develop bronchospasm may not be able to continue administration despite prior bronchodilator administration. Rarely, very severe bronchospasm has been encountered.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long term studies in mice (12 months intraperitoneal treatment followed by 6 months observation), hamsters (12 months intraperitoneal treatment followed by 12 months observation), and rats (18 months subcutaneous treatment) showed no neoplastic effect of cromolyn sodium.

No evidence of chromosomal damage or cytotoxicity was obtained in various mutagenesis studies.

No evidence of impaired fertility was shown in laboratory animal reproduction studies.

Pregnancy: Pregnancy Category B. Reproduction studies with cromolyn sodium administered parenterally to pregnant mice, rats, and rabbits in doses up to 338 times the human clinical doses produced no evidence of fetal malformations. Adverse fetal effects (increased resorptions and decreased fetal weight) were noted only at the very high parenteral doses that produced maternal toxicity. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Drug Interaction During Pregnancy: Cromolyn sodium and isoproterenol were studied following subcutaneous injections in pregnant mice. Cromolyn sodium alone in doses of 60 to 540 mg/kg (38 to 338 times the human dose) did not cause significant increases in resorptions or major malformations. Isoproterenol alone at a dose of 2.7 mg/kg (90 times the human dose) increased both resorptions and malformations. The addition of cromolyn sodium (338 times the human dose) to isoproterenol (90 times the human dose) appears to have increased the incidence of both resorptions and malformations.

Nursing Mothers: It is not known whether this drug is excreted in human milk, therefore, caution should be exercised when INTAL Inhaler is administered to a nursing woman and the attending physician must make a benefit/risk assessment in regard to its use in this situation.

Pediatric Use: Safety and effectiveness in children below the age of 5 years have not been established. For young children unable to utilize the Inhaler, INTAL Nebulizer Solution (cromolyn sodium inhalation, USP) is recommended. Because of the possibility that adverse effects of this drug could become apparent only after many years, a benefit/risk consideration of the long-term use of INTAL Inhaler is particularly important in pediatric patients.

ADVERSE REACTIONS: In controlled clinical studies of INTAL Inhaler, the most frequently reported adverse reactions attributed to cromolyn sodium treatment were: throat irritation or dryness, bad taste, cough, wheeze, nausea.

The most frequently reported adverse reactions attributed to other forms of cromolyn sodium (on the basis of reoccurrence following readministration) involve the respiratory tract and are: bronchospasm [sometimes severe, associated with a precipitous fall in pulmonary function (FEV_1)], cough, laryngeal edema (rare), nasal congestion (sometimes severe), pharyngeal irritation and wheezing.

Adverse reactions which occur infrequently and are associated with administration of the drug are: anaphylaxis, angioedema, dizziness, dysuria and urinary frequency, joint swelling and pain, lacrimation, nausea and headache, rash, swollen parotid gland, urticaria, pulmonary infiltrates with eosinophilia, substernal burning, and myopathy.

The following adverse reactions have been reported as rare events and it is unclear whether they are attributable to the drug: anemia, exfoliative dermatitis, hemoptysis, hoarseness, myalgia, nephrosis, periarteritic vasculitis, pericarditis, peripheral neuritis, photodermatitis, sneezing, drowsiness, nasal itching, nasal bleeding, nasal burning, serum sickness, stomach ache, polymyositis, vertigo, and liver disease.

OVERDOSAGE: No action other than medical observation should be necessary.

DOSAGE AND ADMINISTRATION: For management of bronchial asthma in adults and children (5 years of age and over) who are able to use the Inhaler, the usual starting dosage is two metered sprays inhaled four times daily at regular intervals.

Patients with chronic asthma should be advised that the effect of INTAL Inhaler therapy is dependent upon its administration at regular intervals, as directed. INTAL Inhaler should be introduced into the patient's therapeutic regimen when the acute episode has been controlled, the airway has been cleared and the patient is able to inhale adequately.

For the prevention of acute bronchospasm which follows exercise, exposure to cold dry air or environmental agents, the usual dose is the inhalation of two metered dose sprays shortly, i.e., 10-15 minutes but not more than 60 minutes, before exposure to the precipitating factor.

INTAL INHALER THERAPY IN RELATION TO OTHER TREATMENTS FOR ASTHMA: Non-steroidal agents: INTAL Inhaler should be **added** to the patient's existing treatment regimen (e.g., bronchodilators). When a clinical response to INTAL Inhaler is evident, usually within two to four weeks, and if the asthma is under good control, an attempt may be made to decrease concomitant medication usage gradually.

Corticosteroids: In patients chronically receiving corticosteroids for the management of bronchial asthma, the dosage should be maintained following the introduction of INTAL Inhaler. If the patient improves, an attempt to decrease corticosteroids should be made.

It is particularly important that great care be exercised if for any reason cromolyn sodium is withdrawn in cases where its use has permitted a reduction in the maintenance dose of corticosteroids.

HOW SUPPLIED: INTAL Inhaler, 8.1g or 14.2g canister, box of one. Supplied with inhalation adapter and patient instructions.

NDC 0585-0675-01 14.2g canister
NDC 0585-0675-02 8.1g canister

Store between 2°-30°C (36°-86°F). Contents under pressure. Do not puncture or incinerate. Keep out of the reach of children.

CAUTION: Federal law prohibits dispensing without prescription.

Manufactured for:
FISONS CORPORATION
ROCHESTER, NY 14623 U.S.A.

By:
Riker Laboratories
One Morley Street
Loughborough, England LE11 1EP

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Rev 7/86
FC 7518B

Reference: 1. Eigen H, Reid JJ, Dahl R, et al: Evaluation of the addition of cromolyn sodium to bronchodilator maintenance therapy in the long-term management of asthma. *J Allergy Clin Immunol* 1987;80:612-621.

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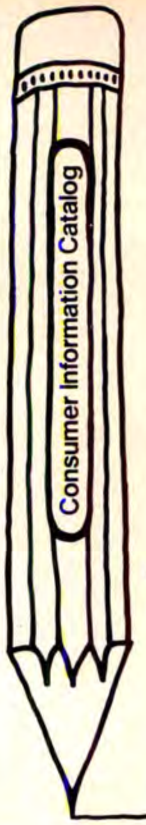

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When it comes to vaccines, MERCK knows how to think small.

Now for most 2-month-olds

PedvaxHIB®

(Haemophilus b Conjugate Vaccine
[Meningococcal Protein Conjugate] | MSD)

The only Haemophilus b vaccine with a 2-dose primary regimen

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A booster dose should be administered in infants completing the primary 2-dose regimen before 12 months of age.

PedvaxHIB is contraindicated in patients who are hypersensitive to any component of the vaccine or the diluent.

For a Brief Summary of Prescribing Information, please see next page

For most infants,

Predictable

PedvaxHIB®

(Haemophilus b Conjugate Vaccine [Meningococcal Protein Conjugate] | MSD)

INDICATIONS AND USAGE: PedvaxHIB is indicated for routine immunization against invasive disease caused by *Haemophilus influenzae* type b in infants and children 2 to 71 months of age.

PedvaxHIB will not protect against disease caused by *Haemophilus influenzae* other than type b or against other microorganisms that cause invasive disease, such as meningitis or sepsis.

Revaccination: Infants completing the primary two-dose regimen before 12 months of age should receive a booster dose (see DOSAGE AND ADMINISTRATION).

Use with Other Vaccines: Studies have been conducted in which PedvaxHIB has been administered concomitantly with the primary vaccination series of DTP and OPV, or concomitantly with M-M-R® II (Measles, Mumps, and Rubella Virus Vaccine Live, MSD) (using separate sites and syringes), or with a booster dose of OPV plus DTP (using separate sites and syringes for PedvaxHIB and DTP). No impairment of immune response to individual tested vaccine antigens was demonstrated. The type, frequency, and severity of adverse experiences observed in these studies with PedvaxHIB were similar to those seen when the other vaccines were given alone.

PedvaxHIB IS NOT RECOMMENDED FOR USE IN INFANTS YOUNGER THAN 2 MONTHS OF AGE.

CONTRAINDICATIONS: Hypersensitivity to any component of the vaccine or the diluent.

WARNINGS: USE ONLY THE ALUMINUM HYDROXIDE DILUENT SUPPLIED. If PedvaxHIB is used in persons with malignancies or in those who are receiving immunosuppressive therapy or who are otherwise immunocompromised, the expected immune response may not be obtained.

PRECAUTIONS: ***General:*** As for any vaccine, adequate treatment provisions, including epinephrine, should be available for immediate use should an anaphylactoid reaction occur. As with other vaccines, PedvaxHIB may not induce protective antibody levels immediately following vaccination. As with any vaccine, vaccination with PedvaxHIB may not result in a protective antibody response in all individuals given the vaccine. As reported with Haemophilus b polysaccharide vaccine and another Haemophilus b conjugate vaccine, cases of Haemophilus b disease may occur in the week after vaccination, prior to the onset of the protective effects of the vaccines. There is insufficient evidence that PedvaxHIB given immediately after exposure to natural *Haemophilus influenzae* type b will prevent illness. Any acute infection or febrile illness is reason for delaying use of PedvaxHIB except when, in the opinion of the physician, withholding the vaccine entails a greater risk.

Laboratory Test Interactions: Sensitive tests (e.g., Latex Agglutination Kits) may detect PRP derived from the vaccine in urine of some vaccinees for up to seven days following vaccination with PedvaxHIB; in clinical studies with PedvaxHIB, such children demonstrated normal immune response to the vaccine.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: PedvaxHIB has not been evaluated for its carcinogenic or mutagenic potential or for its potential to impair fertility.

Pregnancy: *Pregnancy Category C:* Animal reproduction studies have not been conducted with PedvaxHIB. It is also not known whether PedvaxHIB can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. PedvaxHIB is not recommended for use in pregnant women.

ADVERSE REACTIONS: In early clinical studies involving the administration of 8,086 doses of PedvaxHIB alone to 5,027 healthy infants and children 2 months to 71 months of age, PedvaxHIB was generally well tolerated. No serious adverse reactions were reported. During a two-day period following vaccination with PedvaxHIB in a subset of these infants and children, the most frequently reported adverse reactions, excluding those shown in the first table, in decreasing order of frequency, included: irritability, sleepiness, respiratory infection/symptoms, and ear infection/otitis media. Urticaria was reported in two children. Thrombocytopenia was seen in one child. A cause-and-effect relationship between these side effects and the vaccination has not been established.

Selected objective observations reported by parents over a 48-hour period in infants and children 2 to 71 months of age following primary vaccination with PedvaxHIB alone are summarized in the first table.

In The Protective Efficacy Study, 4,459 healthy Navajo infants 6 to 12 weeks of age received PedvaxHIB or placebo. Most of these infants received DTP/OPV concomitantly. No differences were seen in the type and frequency of serious health problems expected in this Navajo population or in serious adverse experiences reported among those who received PedvaxHIB and those who received placebo, and none was reported to be related to PedvaxHIB. Only one serious reaction (tracheitis) was reported as possibly related to PedvaxHIB and only one (diarrhea) as possibly related to placebo. Seizures occurred infrequently in both groups (9 occurred in vaccine recipients, 8 of whom also received DTP; 8 occurred in placebo recipients, 7 of whom also received DTP) and were not reported to be related to PedvaxHIB. The frequencies of fever and local reactions occurring in a subset of these infants during a 48-hour period following each dose were similar to those seen in early clinical studies (see first table).

As with any vaccine, there is the possibility that broad use of PedvaxHIB could reveal adverse reactions not observed in clinical trials.

Potential Adverse Reactions: The use of Haemophilus b polysaccharide vaccines and another Haemophilus b conjugate vaccine has been associated with the following additional adverse effects: early onset of Haemophilus b disease and Guillain-Barré syndrome. A cause-and-effect relationship between these side effects and the vaccination was not established.

Fever or Local Reactions in Subjects 2 to 71 Months of Age Vaccinated with PedvaxHIB Alone: Other Clinical Studies

		Dose 1				Dose 2			
Age (Months)	Reaction	Number of Subjects Evaluated	6 hr.	24	48	Number of Subjects Evaluated	6 hr.	24	48
2-14*	Fever >38.3°C (101°F) Rectal	532	2.4%	3.8%	1.9%	329	3.0%	4.3%	3.6%
	Erythema >2.5 cm diameter	1,026	0.2%	1.0%	0.4%	585	0.9%	1.2%	0.7%
	Swelling/ Induration >2.5 cm diameter	1,026	0.6%	1.5%	1.6%	585	0.9%	2.8%	3.7%
15-71**	Fever >38.3°C (101°F) Rectal	149	4.0%	4.0%	6.7%				
	Erythema >2.5 cm diameter	572	0.0%	0.3%	0.2%				
	Swelling/ Induration >2.5 cm diameter	572	0.9%	2.1%	1.4%				

*Additional complaints reported following vaccination with the first and second dose of PedvaxHIB, respectively, in the indicated number of subjects were: nausea, vomiting, and/or diarrhea (101, 41), crying for more than one-half hour (43, 15), rash (16, 17), and unusual high-pitched crying (4, 4).

**Additional complaints reported following vaccination with one dose of PedvaxHIB in the indicated number of subjects were: nausea, vomiting, and/or diarrhea (44), crying for more than one-half hour (19), rash (12), and unusual high-pitched crying (0).

DOSAGE AND ADMINISTRATION:

FOR INTRAMUSCULAR ADMINISTRATION. DO NOT INJECT INTRAVENOUSLY.

2 to 14 Months of Age: Infants 2 to 14 months of age should receive a 0.5-mL dose of vaccine ideally beginning at 2 months of age followed by a 0.5-mL dose 2 months later (or as soon as possible thereafter). When the primary two-dose regimen is completed before 12 months of age, a booster dose is required (see text and second table).

15 Months of Age and Older: Children 15 months of age and older previously unvaccinated against Haemophilus b disease should receive a single 0.5-mL dose of vaccine.

Booster Dose: In infants completing the primary two-dose regimen before 12 months of age, a booster dose (0.5 mL) should be administered at 12 months of age but not earlier than 2 months after the second dose.

DATA ARE NOT AVAILABLE REGARDING THE INTERCHANGEABILITY OF OTHER HAEMOPHILUS b CONJUGATE VACCINES AND PedvaxHIB® (Haemophilus b Conjugate Vaccine [Meningococcal Protein Conjugate], MSD).

Vaccination Regimens by Age Group
(see text for details)

Age (Months) at First Dose	Primary	Age (Months) at Booster Dose
2-10	2 doses, 2 months apart	12
11-14	2 doses, 2 months apart	—
15-71	1 dose	—

TO RECONSTITUTE, USE ONLY THE ALUMINUM HYDROXIDE DILUENT SUPPLIED.

First, agitate the diluent vial; then, using sterile technique, withdraw the entire volume of aluminum hydroxide diluent into the syringe to be used for reconstitution. Inject all the aluminum hydroxide diluent in the syringe into the vial of lyophilized vaccine, and agitate to mix thoroughly.

Withdraw the entire contents into the syringe and inject the total volume of reconstituted vaccine (0.5 mL) intramuscularly, preferably into the anterolateral thigh or the outer aspect of the upper arm.

It is recommended that the vaccine be used as soon as possible after reconstitution. Store reconstituted vaccine in the vaccine vial at 2° to 8°C (36° to 46°F) and discard if not used within 24 hours. Agitate prior to injection.

Parenteral drug products should be inspected visually for extraneous particulate matter and discoloration prior to administration whenever solution and container permit. Aluminum hydroxide diluent and PedvaxHIB when reconstituted are slightly opaque white suspensions.

Special care should be taken to ensure that the injection does not enter a blood vessel.

It is important to use a separate sterile syringe and needle for each patient to prevent transmission of hepatitis B or other infectious agents from one person to another.

HOW SUPPLIED: No. 4792–PedvaxHIB is supplied as a single-dose vial of lyophilized vaccine, NDC 0006-4792-00, and a vial of aluminum hydroxide diluent.

No. 4797–PedvaxHIB is supplied as follows: a box of 5 single-dose vials of lyophilized vaccine, NDC 0006-4797-00, and 5 vials of aluminum hydroxide diluent.

Storage: Before reconstitution, store PedvaxHIB at 2° to 8°C (36° to 46°F). Store reconstituted vaccine in the vaccine vial at 2° to 8°C (36° to 46°F) and discard if not used within 24 hours.

DO NOT FREEZE the aluminum hydroxide diluent or the reconstituted vaccine.

For more detailed information, consult your MSD Representative or see Prescribing Information.

Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, PA 19486.

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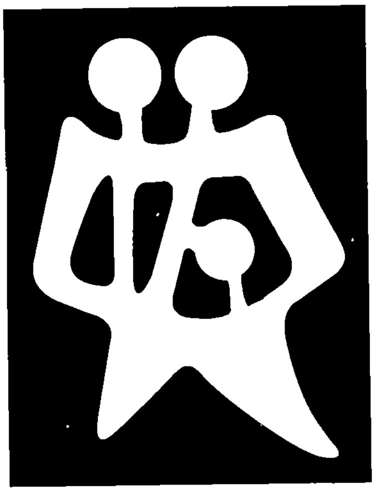

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APA Application for Membership

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The objectives of the Ambulatory Pediatric Association are to improve the teaching of general pediatrics, to improve research in general pediatrics, to improve patient services in general pediatrics, and to affect public and governmental opinion regarding issues vital to teaching and research in general pediatrics. Applications for membership will be considered from members of the health care professions involved in teaching and patient care or research in general pediatrics.

Application forms are obtained from the Executive Secretary's Office:

Executive Secretary
Ambulatory Pediatric Association
6728 Old McLean Village Dr
McLean, VA 22101
(703) 556-9222

Future Annual Meetings

1992—*May 4-8, Baltimore Convention Center, Baltimore, Md*
1993—*May 3-7, Sheraton Hotel, Washington, DC*
1994—*May 2-5, Seattle Convention Center, Seattle, Wash*
1995—*May 8-12, San Diego, Calif*
1996—*May 6-10, Washington, DC*

APA PROGRAM SCHEDULE

Sunday, April 28

Time	Event	Room
5 PM-10 PM	APA Board of Directors Meeting	Oak Alley

Monday, April 29

Time	Event	Room
8 AM-NOON	*APA Board of Directors Meeting*	Melrose
3:30 PM-7 PM	*Poster Session APA/APS/SPR (p 373)*	South Hall Rivergate Convention Center
7 PM-8 PM	*Opening Reception APA/APS/SPR*	South Hall Rivergate Convention Center

Tuesday, April 30

Time	Event	Room
7:30 AM-9 AM	*Past Officers Breakfast*	Belle Chasse
	APA Special Interest Groups	
8 AM-NOON	Clerkship Directors	Marlborough Suite
	Emergency Medicine	Versailles
9 AM-NOON	*APA Special Interest Groups*	
	Women in Medicine	Cambridge
	International Health	Grand Salon Section 3
	Residency Program Directors	Prince of Wales
	Serving the Underserved	Grand Salon Section 6
	APA Workshops 1-10 (p 372)	
	Workshop 1	Oak Alley
	Workshop 2	Newberry
	Workshop 3	Eglington & Winton
	Workshop 4	Norwich
	Workshop 5	Durham
	Workshop 6	Jasperwood
	Workshop 7	Burgundy
	Workshop 8	Magnolia
	Workshop 9	Chequers
	Workshop 10	Grand Salon Section 4
NOON-2 PM	*APA Regional Chairs Luncheon*	Trafalgar
	APA SIG Chairs Luncheon	Ascot
2:40 PM-3 PM	*St. Geme Award*	Grand Ballrooms A&B
3 PM-6:30 PM	*APA/APS/SPR Joint Topic Sessions (p 374)*	
	Adolescent Medicine	Grand Ballroom C
	Behavioral Pediatrics	Grand Salon D
	Epidemiology & Preventive Pediatrics	Grand Salon C
	General Pediatrics & Pediatric Education	Grand Ballroom D
6:30 PM-8:30 PM	*APA Committees*	
	Child Health Care Delivery	Newberry
	Research	Norwich
	Education	Durham
	Public Policy	Ascot
	Communications	Warwick

Wednesday, May 1

Time	Event	Room
7:30 AM-9 AM	*APA Regional Breakfast Meetings*	
	Region I	Durham
	Region II	Elmwood
	Region III	Cambridge
	Region IV	Norwich
	Region V	Magnolia
	Region VI	Newberry
	Region VII	Prince of Wales
	Region VIII	Ascot
	Region IX	Eglington & Winton
	Region X	Chequers
9 AM-NOON	*APA Topic Plenary Session (p 377)*	
	Clinical Issues	Grand Ballroom C
	Developmental & Behavioral Pediatrics	Grand Salon A
	Emergency Medicine & Child Abuse	Grand Salon B
	General Pediatrics	Grand Salon C
	Prevention & Epidemiology	Grand Salon D

APA Program Schedule

Time	Event	Room
1:30 PM-4:30 PM	*APA Workshops 11-20 (p 372)*	
	Workshop 11	Jasperwood
	Workshop 12	Cambridge
	Workshop 13	Eglington & Winton
	Workshop 14	Newberry
	Workshop 15	Ascot
	Workshop 16	Norwich
	Workshop 17	Burgundy
	Workshop 18	Durham
	Workshop 19	Elmwood
	Workshop 20	Trafalgar
	APA Special Interest Groups	
	Adolescent Medicine	Rosedown
	AIDS	Chequers
	Behavioral Pediatrics	Magnolia
	Child Abuse	Prince of Wales
	Injury Control	Oak Alley
	Primary Care	Melrose
4:45 PM-6:45 PM	*APA Awards & Business Meeting*	Grand Salon C
	APA Research Award	
	APA Teaching Award	
	APA Business Meeting	
8:30 PM-10 PM	*APA Debate*	Grand Salon A

Thursday, May 2

Time	Event	Room
8 AM-Noon	*APA General Plenary Session (p 379)*	Grand Salon D
	Distinguished Career Award	
	President's Address	
1:30 PM-4:30 PM	*APA Workshops 21-30 (p 373)*	
	Workshop 21	Jasperwood
	Workshop 22	Ascot
	Workshop 23	Newberry
	Workshop 24	Durham
	Workshop 25	Magnolia
	Workshop 26	Cambridge
	Workshop 27	Trafalgar
	Workshop 28	Chequers
	Workshop 29	Eglington & Winton
	Workshop 30	Prince of Wales
	APA Special Interest Groups	
	Chronic Illness	Elmwood
	Continuity Clinic	Rosedown
	Day Care	Melrose
	Homeless Children	Oak Alley
	Nutrition	Norwich
5:15 PM-6 PM	*APA Armstrong Award*	Grand Ballroom C
6 PM-7 PM	*APA Reception*	Melrose

Friday, May 3

Time	Event	Room
8 AM-2 PM	APA Board of Directors Meeting	Oak Alley

Registration Hours

Sunday, April 28	Noon-5 PM
Monday, April 29	8 AM-8 PM
Tuesday, April 30	7 AM-8 PM
Wednesday, May 1	7 AM-6 PM
Thursday, May 2	7:30 AM-5 PM
Friday, May 3	8 AM-Noon

Workshop Registration

Tuesday, April 30	7:15 AM-6 PM
Wednesday, May 1	7:15 AM-5:30 PM
Thursday, May 2	7:15 AM-12:30 PM

As an organization accredited for continuing medical education, the America Academy of Pediatrics designates this continuing medical activity as meeting the criteria for 43.5 credit hours in category 1 of the Physician's Recognition Award of the American Medical Association. To those currently enrolled in the American Academy of Pediatrics PREP program, this course is eligible for 43.5 PREP credits.

The California State Board of Registered Nursing has approved this program for 23 Continuing Education Credits for Registered Nurses. Certificates will be available at the APA registration desk.

Ambulatory Pediatric Association 1990-1991

Officers

President	*Carol Berkowitz, MD,* Torrance, Calif
President-Elect	*Kathleen G. Nelson, MD,* Birmingham, Ala
Secretary-Treasurer	*Thomas G. DeWitt, MD,* Worcester, Mass
Immediate Past President	*Paul McCarthy, MD,* New Haven, Conn
Newsletter Editor	*John M. Pascoe, MD, MPH,* Madison, Wis

Board of Directors

uth T. Gross, MD, Stanford, Calif
ohn M. Leventhal, MD, New Haven, Conn
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obert H. Pantell, MD, San Francisco, Calif
odena E. H. Wilson, MD, MPH, Baltimore, Md

Past Presidents

1961-1962	*Richard W. Olmsted*
1962-1963	*Morris Green*
1963-1964	*Robert J. Haggerty*
1964-1965	*Frederic M. Blodgett*
1965-1966	*Donal Dunphy*
1966-1967	*Loren G. MacKinney*
1967-1968	*Lewis M. Fraad*
1968-1969	*Hugo Dunlap Smith*
1969-1970	*Joel J. Alpert*
1970-1971	*John H. Kennell*
1971-1972	*Donald Fink*
1972-1973	*Ray E. Helfer*
1973-1974	*Katherine S. Lobach*
1974-1975	*Evan Charney*
1975-1976	*Frederick North, Jr.*
1976-1977	*Margaret C. Heagarty*
1977-1978	*Robert Hoekelman*
1978-1979	*George Comerci*
1979-1980	*Ivan Barry Pless*
1980-1981	*Barbara Starfield*
1981-1982	*Alvin Novack*
1982-1983	*Philip Nader*
1983-1984	*Fredric D. Burg*
1984-1985	*Abraham B. Bergman*
1985-1986	*Catherine DeAngelis*
1986-1987	*Jay E. Berkelhamer*
1987-1988	*Ruth E. K. Stein*
1988-1989	*Steven P. Shelov*
1989-1990	*Paul McCarthy*

Regional Chairs

I.	*William G. Bithoney, MD,* West Roxbury, Mass
II.	*Alan B. Bernstein, MD,* Brooklyn, NY
	Mary Ann LoFrumento, MD, Morristown, NJ
III.	*Kenneth M. McConnochie, MD,* Rochester, NY
IV.	*Gregory Hayden, MD,* Charlottesville, Va
V.	*John Chessare, MD, MPH,* Toledo, Ohio
	Daniel Coury, MD, Columbus, Ohio
VI.	*Timothy Russell Schum, MD,* Milwaukee, Wis
	Patricia S. Simmons, MD, Rochester, Minn
VII.	*Pamela Wood, MD,* San Antonio, Tex
VIII.	*Joseph Pesek, MD,* Jacksonville, Fla
IX.	*Sandra L. Elvik, MS, CPNP,* Torrance, Calif
	Stanley Howard Inkelis, MD, Los Angeles, Calif
X.	*Kathi Kemper, MD,* Seattle, Wash

Past Secretary-Treasurers

1961-1963	*Frederic M. Blodgett*
1963-1966	*Hugo Dunlap Smith*
1966-1969	*Abraham B. Bergman*
1969-1972	*Katherine S. Lobach*
1972-1974	*Elizabeth S. Hillman*
1974-1977	*George Comerci*
1977-1980	*Fredric D. Burg*
1980-1983	*Barbara Durand*
1983-1986	*Marie McCormick*
1986-1989	*Kathleen Nelson*

APA Teaching Award

The purpose of this award is to foster interest in the teaching of ambulatory pediatrics by giving national recognition to an outstanding ambulatory pediatric program. Programs must demonstrate excellence in educational teaching methods, acceptance by students and/or residents, acceptance by the community and the institution, innovations and adaptability, or outstanding quality of the individuals trained in the program. Emphasis is placed on the award being given to *an* outstanding *program.*

1972 University of Arizona
College of Medicine
Department of Pediatrics
Division of Ambulatory Pediatrics
Tucson

1976 University of Chicago
Pritzker School of Medicine
Wyler Children's Hospital
Division of Ambulatory Pediatrics

1977 University of Vermont
College of Medicine
Department of Pediatrics
Division of Ambulatory Pediatrics
Burlington, Vt

1978 Children's Hospital of Philadelphia
Division of Ambulatory Services
Resident Group Practice

1980 Primary Care Training Program
Department of Pediatrics
University of Arizona
College of Medicine
Tucson

1981 Sinai Hospital of Baltimore
Pediatric Residency Training Program

1982 Child Health Associate Program
University of Colorado
Health Sciences Center
Denver

1984 University of North Carolina—Chapel Hill
Department of Pediatrics
Community Outreach Training Program

1986 Pediatric Practice Model
University of Oklahoma College of Medicine
Oklahoma City

1987 Chronic Illness Teaching Program
Department of Pediatrics and
Human Development
Michigan State University
East Lansing

1988 Emergency Room Teaching Program
Children's Hospital of Philadelphia (Pa)
and
Behavioral and Developmental
Pediatric Fellowship Program
Department of Pediatrics
Ohio State University
Columbus

1989 Primary Care Training Program
University of California—
San Diego Department of Pediatrics
Division of General Pediatrics

1990 Behavioral Science Training Program
University of California—San Francisco

1991 University of Utah Pediatric Residency Program
University of Utah Center for Health Sciences
and the
Primary Children's Medical Center
and
Third Year Pediatric Clerkship (MS III)
Department of Pediatrics
F. Edward Hebert School of Medicine
Uniformed Services University of the
Health Sciences

APA Awards

APA RESEARCH AWARD

The APA Research Award acknowledges the contribution of an individual in advancing pediatric knowledge through excellence in research. Research excellence is characterized by originality, creativity, and methodological soundness. The findings should contribute significantly to the general health of children in such areas as understanding mechanisms of health and disease, methods of education, and innovative ways of providing children's services.

1990 ***Barbara Starfield***

1991 ***Ivan Barry Pless***

APA DISTINGUISHED CAREER AWARD

The APA Distinguished Career Award recognizes members of the Association who have fostered the goals of the APA throughout their careers. They have distinguished themselves in the promotion of improved patient care, teaching, and research in ambulatory pediatrics.

1991 ***Barbara M. Korsch***

The George Armstrong Lectures

George Armstrong, an English physician of the 18th century, established the first dispensary for children in London, England, in 1769. There he served with great devotion and taught others the care of sick children. He is honored as one of the fathers of modern pediatrics, and those who deliver this lecture are also honored as outstanding teachers and contributors to our knowledge of the care of children.

The lecture is sponsored by Ross Laboratories, Columbus, Ohio.

1967	George A. Silver
1968	Allan M. Butler
1969	Robert H. Haggerty
1970	Julius B. Richmond
1971	Morris Green
1972	Henry K. Silver
1973	Barbara M. Korsch
1974	Lewis Fraad
1975	C. Henry Kempe
1976	Abraham B. Bergman Waldo Nelson
1977	Wilbur J. Cohen
1978	Richard W. Olmsted
1979	John H. Kennell (Children's Defense Fund)
1980	OXFAM (Tim Lusty)
1981	Benjamin Spock
1982	Evan Charney
1983	Barbara Starfield
1984	Victor Vaughan
1985	Gerold L. Schiebler
1986	Marian Wright Edelman
1987	Robert A. Hoekelman
1988	Ivan Barry Pless
1989	Joel J. Alpert
1990	Catherine DeAngelis
1991	Paul L. McCarthy

APA Workshops and Special Interest Groups

Tuesday, April 30, 1991
9 AM-NOON

1. **Federal Funding for Health Services Research in Primary Care** *Oak Alley*
   Leaders: *P. A. Nutting and B. A. White*
2. **Evaluation Research: The Impossible Made Easy** *Newberry*
   Leaders: *L. J. Bauman and R. E. K. Stein*
3. **Logistic Regression: A Guide for the Slightly Perplexed** *Eglington & Winton*
   Leaders: *P. Margolis and S. Goodman*
4. **Sex Education in Adolescents with Chronic Diseases and Disabilities** *Norwich*
   Leaders: *B. A. Cromer, S. J. Rost, and M. J. Gerhardstein*
5. **Foster Children—Meeting Their Health Care Needs** *Durham*
   Leaders: *R. Chernoff, H. Dubowitz, D. Chadwick, M. Simms, and N. Kaufman*
6. **Pediatricians Facilitation of Healthy Sexual Development With Families** *Jasperwood*
   Leaders: *C. A. Croft and M. C. Sorrentino*
7. **Primate Parallels: Mothers, Infants and Love** *Burgundy*
   Leader: *R. E. Helfer*
8. **"Please Don't Die on My Shift"—Helping the Pediatrician Deal With Patient Death** *Magnolia*
   Leaders: *D. J. Timmel and D. J. Schonfeld*
9. **Children and Venipuncture: Coping Skills for Professionals and Patients** *Chequers*
   Leaders: *M.H. Young, S. Franklin, N. Powers, and D. Moiles*
10. **Society for Behavioral Pediatrics Workshop: Child Development Projects: Collaboration Between Educators and Pediatricians** *Grand Salon Section 4*
    Leaders: *B. Zuckerman, M. Kaplan-Sanoff, R. Needlman, and K. Bresnahan*

Special Interest Groups

Clerkship Directors *(8 AM-NOON)*	*Marlborough Suite*
Emergency Medicine *(8 AM-NOON)*	*Versailles*
Women in Medicine	*Cambridge*
International Health	*Grand Salon Section 3*
Residency Program Directors	*Prince of Wales*
Serving the Underserved	*Grand Salon Section 6*

Wednesday, May 1, 1990
1:30 PM-4:30 PM

11. **New Concepts in the Screening, Management, and Neurotoxicity of Childhood Lead Poisoning** *Jasperwood*
    Leaders: *J. W. Graef, M. Shannon, and D. Bellinger*
12. **Schools and Day Care Centers: Innovative Settings for Residency Training** *Cambridge*
    Leaders: *E. C. Allen, L. S. Grossman, and J. C. Joost*
13. **Community-Based Continuity Clinic Programs: Practical Approaches to Implementation** *Eglington & Winton*
    Leaders: *L. M. Osborn, J. R. Sargent, S. D. Williams, T. G. DeWitt, and K. B. Roberts*
14. **Child Development, Pain, and Mental Imagery** *Newberry*
    Leaders: *R. Solomon and C. Saylor*
15. **Preparing Interns for Residency: A "Teaching and Leadership" Seminar** *Ascot*
    Leaders: *J. Anderson, C. Chantry, R. Kamei, and K. Overby*
16. **Stayin' Alive in Pediatric Emergency Medicine** *Norwich*
    Leaders: *S. Selbst, F. Henretig, S. Ludwig, K. Shaw, and C. McAneney*
17. **Quality Assurance in the Emergency Department** *Burgundy*
    Leaders: *F. Oberklaid and F. Jarman*
18. **Problem-Based Learning in Pediatrics** *Durham*
    Leaders: *F. A. McCurdy, J. O. Lopreiato, C. B. White, and B. A. DeFrancesco*
19. **Resuscitating Your Continuity Clinic** *Elmwood*
    Leaders: *J. E. Drutz, D. Kittredge, D. C. Hurley, C. R. Reed, R. M. Rutstein, R. C. Baker, L. R. First, J. N. Middlekamp, and M. E. H. Wilson*
20. **An Academic Seminar: Beyond Epidemiology and Biostatistics** *Trafalgar*
    Leaders: *H. Bauchner, J. Howland, and R. Needlman*

Special Interest Groups

Adolescent Medicine	*Rosedown*
AIDS	*Chequers*
Behavioral Pediatrics	*Magnolia*
Child Abuse	*Prince of Wales*
Injury Control	*Oak Alley*
Primary Care	*Melrose*

APA Workshops and Special Interest Groups

Thursday, May 2, 1991
1:30 PM-4:30 PM

21. **Anatomy and Physiology of Successful Residency Educational Programs: What We Can Learn and Apply Back Home** *Jasperwood*
Leaders: *J. M. Devries and L. Osborn*

22. **How to Write an Abstract** *Ascot*
Leaders: *K. J. Kemper and F. P. Rivara*

23. **Sample Size Estimation for Clinical Research** *Newberry*
Leader: T. B. Newman

24. **The Medical Interview and Clinical Problem Solving as an Educational Orientation for Medical Students and House Officers** *Durham*
Leaders: *A. P. Scheiner and B. Siegel*

25. **Reinterpreting Disability: Origins and Consequences of the Supreme Court SSI Decision** *Magnolia*
Leaders: *J. M. Perrin, R. E. K. Stein, and S. Davis*

26. **Integration of International Child Health Training into Undergraduate and Graduate Pediatric Programs** *Cambridge*
Leaders: *A. Brann, B. Duncan, J. Ey, J. Goldhagen, R. Hill, and R. Pust*

27. **Teaching Residents the Fundamentals of the Sexual Abuse Evaluation Towards a Comprehensive Curriculum** *Trafalgar*
Leaders: *A. Giardino, C. Christian, T. Seidl, W. Schwartz, and S. Ludwig.*

28. **Use of Computer Simulations to Expand the Teaching of General Pediatrics** *Chequers*
Leader: W. Schwartz

29. **Wound Management for the Pediatrician: Abrasions to Z-Plasty** *Eglington & Winton*
Leaders: *L. S. Fitzmaurice, J. F. Knapp, and T. M. Barnett*

30. **Law and Order in the Emergency Department—Avoiding Hill Street Blues** *Prince of Wales*
Leaders: *S. Selbst, S. Ludwig, J. Loiselle, and C. Barcliff*

Special Interest Groups

Chronic Illness	*Elmwood*
Continuity Clinic	*Rosedown*
Day Care	*Melrose*
Homeless Children	*Oak Alley*
Nutrition	*Norwich*

General Poster Session

Monday, April 29, 1991
3:30 PM-7 PM
South Hall and Rivergate Convention Center

147 **Direct Bilirubin Measurements in Jaundiced Term Newborns: A Waste of Blood and Money?** *T. B. Newman, S. Hope, and D. K. Stevenson. General Pediatrics and Epidemiology, University of California, San Francisco, and Stanford University, San Francisco.*

148 **Home Phototherapy—Use and Attitudes Among Community Pediatricians.** *S. B. Meropol, A. A. Luberti, A. R. DeJong, and J. C. Weiss. Department of Pediatrics, Jefferson Medical College, Philadelphia, Pa.*

149 **The Health Status of Children Placed with Relatives.** *H. Dubowitz, S. Feigelman, S. Zuravin, V. Tepper, R. Lichenstein, and N. Davidson. Department of Pediatrics, University of Maryland Medical School, Baltimore.*

150 **Foster Children: Predictors of Developmental Problems on Baseline Health Assessment.** *S. M. Horwitz and M. D. Simms. Yale University, Department of Epidemiology and Public Health, New Haven, Conn, and Foster Care Clinic, St Mary's Hospital, Waterbury, Conn.*

151 **Measurement of Gestational Cocaine Exposure.** *C. M. Callahan, T. M. Grant, P. Phipps, G. D. Clark, A. H. Novack, A. P. Streissguth, and V. A. Raisys. University of Washington, Seattle.*

152 **Effects of Head Start on Children with Lead Poisoning.** *B. Howard and E. Charney. Department of Pediatrics, Duke University Medical Center, Durham, NC, and Department of Pediatrics, University of Massachusetts Medical Center, Worcester.*

153 **Elevated Lead (Pb) Levels in Abused Children.** *W. Bithoney, W. Barbaresi, A. Vandeven, and A. Ryan. Children's Hospital, Department of Medicine, Boston, Mass.*

154 **Getting Away with Murder? A Study of Unintentional Child Shootings.** *J. T. Maurer, M. J. Barthel, and R. R. Tanz. Department of Pediatrics, Children's Memorial Hospital, Northwestern University Medical School, Chicago, Ill.*

155 **Patterns of Causation for Intentional Injury in a Population Based Study of Urban Children.** *L. L. Davidson, M. S. Durkin, P. O'Connor, B. Barlow and M. C. Heagarty. Departments of Pediatrics, Pediatric Surgery, and Public Health, Columbia University, New York, NY, and Russell Sage College, Troy, NY.*

156 **Physician Decisions to Report and Label Suspected Child Maltreatment.** *L. S. Wissow, M. E. H. Wilson, and G. L. Zellman. Department of Pediatrics, Johns Hopkins University School of Medicine, Baltimore, Md, and The Rand Corporation, Santa Monica, Calif.*

157 **Sexual Abuse by Father-Figures: A Comparison of Natural Fathers, Stepfathers, and Mothers' Paramours.** *A. R. DeJong. Department of Pediatrics, Jefferson Medical College of Thomas Jefferson University, Philadelphia, Pa.*

158 **An Association Between Sexual Abuse and Early Adolescent Pregnancy.** *J. E. Cox, L. Coyne, and W. G. Bithoney. Department of Pediatrics, Harvard Medical School and Children's Hospital, Boston, Mass.*

159 **Utilization of Prenatal Care by Adolescents: Who Starts When?** *M. C. Pew, J. M. Leventhal, and S. M. Horwitz. Department of Pediatrics, Yale University School of Medicine, New Haven, Conn.*

160 **Adolescent AIDS Education in a Pediatric Emergency Department.** *A. J. Behrman, K. N. Shaw, and F. S. Shofer. Departments of Internal Medicine and Pediatrics, University of Pennsylvania School of Medicine, Philadelphia.*

161 **Clinical Utility of *Chlamydia Trachomatis* Diagnostic Techniques in Adolescent Women.** *F. M. Biro, S. F. Reising, and J. A. Doughman. Department of Pediatrics, Children's Hospital Medical Center, University of Cincinnati (Ohio).*

162 **Peer Screeners to Identify Substance Abuse in Pregnant Teens.** *S. Barnett, D. P. McCormick, G. Wilkinson, and A. Berensen. Departments of Pediatrics, Preventive Medicine/Community Health and Obstetrics, University of Texas Medical Branch, Galveston.*

General Poster Session

163 **PID: Evaluation and Treatment in a Pediatric vs Adult Emergency Department.** *J. M. Lavelle, I. Reyes, and K. N. Shaw. Department of Pediatrics, University of Pennsylvania School of Medicine, The Children's Hospital of Philadelphia, and the Hospital of the University of Pennsylvania, Philadelphia.*

164 **Prior Advice Seeking and Appropriate Use of a Pediatric Emergency Room.** *T. F. Oberlander, I. B. Pless, G. E. Dougherty, and D. McGillivray. Department of Pediatrics, McGill University, Montreal, Quebec.*

165 **Prehospital IV Placement in Children.** *K. A. Grisanti and D. M. Jaffe. Department of Pediatrics, Hospital for Sick Children, University of Toronto (Ontario).*

166 **Responses of Children, Parents, and Nurses to Tympanic Thermometry in the Pediatric Office.** *D. T. Alexander and B. A. Kelly. Department of Pediatrics, University of Pennsylvania School of Medicine, Philadelphia, and Children's Hospital of Philadelphia.*

167 **Effect of Personalized Letter Reminders on Preventive Appointment Show Rates and Vaccination Status.** *J. R. Campbell, P. G. Szilagyi, L. E. Rodewald, C. B. Doane, and K. J. Roghmann. Department of Pediatrics, University of Rochester (NY), Strong Memorial Hospital, Rochester.*

168 **Metal Detectors—An Alternative Approach to the Evaluation of Coin Ingestions in Children?** *S. P. Ros and F. Cetta. Pediatrics, Loyola University Medical Center, Maywood, Ill.*

169 **Efficacy of Cough Suppressants in Treating Nighttime Cough in Children.** *J. A. Taylor, A. H. Novack, J. R. Almquist, and J. E. Rogers. Department of Pediatrics, University of Washington, Seattle, and Carolinas Medical Center, Charlotte, NC.*

170 **Milder Symptoms Occur in Recurrent Episodes of Streptococcal Infection.** *K. A. Woodin, L. H. Lee, and M. E. Pichichero. Department of Pediatrics, University of Rochester, (NY).*

171 **Strategies for Diagnosis (Dx) and Treatment of Febrile Infants: Clinical and Cost-Effectiveness.** *T. A. Lieu, M. N. Baskin, J. S. Schwartz, and G. R. Fleisher. Department of Pediatrics, University of Pennsylvania, Philadelphia.*

172 **Blood Culture in the Outpatient Setting: What is the Optimum Number & Method?** *K. J. DiPasquale, G. G. Gaar, and A. B. Anderson. The Emergency Associates for Medicine, The Tampa (Fla) General Hospital.*

173 **Diagnostic Test Ordering in the Evaluation of Febrile Children: The Role of Physician and Environmental Factors.** *D. L. McGillivray, R. Roberts-Brauer, and M. S. Kramer. Departments of Pediatrics and Epidemiology and Biostatistics, McGill University, Montreal, Quebec.*

174 **Management of Febrile Infants by Practicing Pediatricians.** *D. Bergman, R. Pantell, S. Brotherton, and the PROS Network of the AAP. Department of Pediatrics, University of California, San Francisco.*

175 **The Value of Early Treatment for the Prevention of Lyme Disease.** *F. Agre and R. M. Schwartz. Department of Pediatrics, College of Physicians and Surgeons, Columbia University, New York, NY.*

176 **Adaptive Behavior in Subgroups of Children with Attention Deficit Disorder and Hyperactivity Disorder (ADHD).** *N. J. Roizen, T. A. Blondis, and M. Stein. Department of Pediatrics, University of Chicago (Ill) Pritzker School of Medicine, Wyler Children's Hospital, Chicago.*

177 **Who Provides Health Care to the Children of Physicians?** *L. Dusdieker, J. Murph, C. Dungy, and W. Murph. Department of Pediatrics, University of Iowa Hospitals and Clinics, Iowa City.*

178 **Vulnerable Infants and Doctor-Shopping: Common Psychosocial Determinants?** *A. Okun and R. E. K. Stein. Department of Pediatrics, Albert Einstein College of Medicine, Division of Ambulatory Pediatrics, Bronx (NY) Municipal Hospital Center.*

179 **Agreement of the Mother's and Physician's Perception of the Child's Health Status Correlates with Clinic and Emergency Room Use.** *M. Irigoyen and M. Goldstein. Department of Pediatrics, Babies Hospital and Columbia University, New York, NY.*

180 **Parenting Stress in Families of Urban Third Graders.** *L. S. Grossman, M. M. Kappelman, and R. G. Chernoff. Department of Pediatrics, University of Maryland School of Medicine, Baltimore.*

181 **Maternal Emotional Response to Low Birthweight vs Healthy Infants: Role of Social Support.** *S. J. Hershman, H. T. Ireys, and E. J. Silver. Pediatrics, Albert Einstein College of Medicine, Preventive Intervention Research Center, Bronx, NY.*

182 **Third Trimester Maternal Psychosocial Factors and Home Stimulation for Four Month Old Infants: A Prospective Study.** *J. M. Pascoe and J. French. Department of Pediatrics, University of Wisconsin, Madison, and Department of Human Ecology, Michigan State University, East Lansing.*

183 **The Prevalence of Behavioral and Psychosocial Problems in Pediatric Practices.** *P. J. Leaf, S. M. Horwitz, J. M. Leventhal, and K. N. Speechley. Department of Epidemiology and Public Health, Yale University School of Medicine, New Haven, Conn.*

184 **The Relationship Between Maternal Self-Reported Health Status and Maternal Report of Children's Health Status Among Hispanics.** *F. Mendoza, G. Takata, K. Baisden, L. Herrera, and R. Mortorell. Department of Pediatrics and Food Research Institute, Stanford (Calif) University.*

185 **Life Change Events, Disease Course, ESR, and CPR in Patients with Juvenile Arthritis.** *D. M. Siegel, J. Baum, and S. P. Ellis. Department of Pediatrics, University of Rochester (NY) School of Medicine and Dentistry.*

186 **The Preceptor Report Form: An Assessment Tool for Use in Evaluating Residents in Ambulatory Pediatric Settings.** *J. K. Davis and B. Hermosa. Department of Pediatrics, New York (NY) Medical College and Lincoln Medical and Mental Health Center, Bronx, NY.*

187 **The Care Giving Role: Influences of Residents' Background Characteristics.** *M. E. Zondorak-Perez and R. E. K. Stein. Department of Pediatrics, Albert Einstein College of Medicine, Division of Ambulatory Pediatrics, Bronx (NY) Municipal Hospital Center.*

188 **Medicaid During the Reagan Years: Federal and State Reforms.** *J. D. C. Cartland. Department of Research, American Academy of Pediatrics, Elk Grove Village, Ill.*

189 **Linking Medicaid and Special Education in a Rural State.** *C. Field, R. Kirby, and T. Nosal. Department of Pediatrics, University of Arkansas for Medical Sciences, Little Rock.*

Joint Topic Sessions

With American Pediatric Society and Society for Pediatric Research

Tuesday, April 30, 1991
3 PM-6:30 PM

ADOLESCENT MEDICINE

Grand Ballroom C

Moderators: *Robert H. DuRant, PhD, Martin Fisher, MD, and Elizabeth R. McAnarney, MD*

3:00 ***Gender Differences in Establishing Causal Paths for Self Esteem.** *S. K. Steinmetz and D. P. Orr. Departments of Sociology and Pediatrics, Indiana University, Indianapolis.*

3:15 ***Late Pubertal Maturation is Associated with Less Behavioral Risk.** *D. P. Orr, M. Beiter, J. Ryser, and G. M. Ingersoll. Department of Pediatrics, Indiana University School of Medicine, Indianapolis.*

3:30 ***Street Youth: A Heterogeneous Population.** *N. E. MacDonald, S. I. Davidson, B. Ferguson, G. Wells, W. A. Fisher,* *D. Tate, W. Warren, J. A. Doherty, and W. R. Bowie. CYAS Research Group, Children's Hospital of Eastern Ontario, Ottawa.*

Access to Handguns Among Urban Adolescents. *C. M. Callahan and F. P. Rivara. Department of Pediatrics, University of Washington, and Harborview Injury Prevention and Research Center, Seattle.*

***HIV Seroprevalence Rates in Sexually Active Adolescent Members of a Health Maintenance Organization.** *A. Tipton, S. Black, and L. Hurley. Department of Pediatrics, Kaiser Permanente Medical Center, Oakland, Calif.*

***The Impact of AIDS on a Population of Urban Adolescents: Implications for Intervention.** *K. J. Overby and S. M. Kegeles. Departments of Pediatrics and Medicine, University of California, San Francisco.*

Risk Factors for Repeat Adolescent Childbirth. *L. B. Heery, M. J. Werner, and R. M. Brayden. Department of Pediatrics, Division of Community Pediatrics, Vanderbilt University, Nashville, Tenn.*

5 **Predictors of Depression and Substance Abuse in Adolescent Offspring of Former Teenage Mothers.** *S. M. Horwitz, L. V. Klerman, and J. F. Jekel. Department of Epidemiology and Public Health, Yale University School of Medicine, New Haven, Conn.*

0 ***Rurality and Patterns of Early Adolescent Alcohol Use.** *K. J. Kelleher, V. Rickert, B. Hardin, and S. Pope. University of Arkansas for Medical Sciences and Department of Pediatrics, Arkansas Children's Hospital, Little Rock.*

5 ***Patterns of Smokeless Tobacco Use by Early Adolescents.** *V. I. Rickert, A. A. Gottlieb, S. K. Pope, and B. H. Hardin. University of Arkansas for Medical Sciences and Department of Pediatrics, Arkansas Children's Hospital, Little Rock.*

0 ***The Virginal Male Adolescent: Differences in Attitudes and Knowledge?** *K. A. Woodward, L. J. D'Angelo, P. R. Getson, and C. O. Brasseux. Children's National Medical Center, Washington, DC.*

5 ***Factors Associated with High School Students' Attrition from Organized Sports.** *R. H. DuRant, R. A. Pendergrast, J. Donner, C. Seymore, and G. L. Gaillard. Department of Pediatrics, Medical College of Georgia, Augusta, Ga.*

0 **Evaluation of Sexual Behavior in Sports Preparticipation Examination.** *B. J. Foch, M. K. Oh, C. H. Hong, B. C. Cotton, B. C. Brown, and R. A. Feinstein. Department of Pediatrics, University of Alabama, Birmingham.*

15 ***Mental Health Effects of a Social Skills Intervention for Adolescents with Chronic Illness.** *S. M. Coupey, L. J. Bauman, J. L. Lauby, C. R. Koeber, and R. E. K. Stein. PreventiveIntervention Research Center, Department of Pediatrics, Albert Einstein College of Medicine, Bronx, NY.*

BEHAVIORAL PEDIATRICS

Grand Salon D

Moderators: *Daniel Coury, MD, Morris Green, MD, and Sheridan Phillips, PhD*

:00 **The Cry of Colic Facies.** *R. G. Barr, A. Rotman, J. Yaremko, D. Leduc, T. E. Francoeur, and B. Katchan. Department of Pediatrics, McGill University, and Montreal Children's Hospital, Montreal, Quebec.*

:15 ***Infant Cry Analysis Predicts Developmental Outcome in Term and Preterm Infants.** *B. Lester, C. F. Z. Boukydis, M. Corwin, C. Sepkoski, M. Peucker, and H. Golub. Brown University Bradley, and Women and Infants' Hospital, Boston (Mass) University and Cry Research, Inc.*

3:30 ***Predictor of Failure to Thrive in Low Birth Weight Infants.** *K. J. Kelleher, P. Casey, R. Bradley, M. Swanson, L. Whiteside, S. Pope, and K. Barrett. Infant Health and Development Program, Department of Pediatrics, University of Arkansas Medical Sciences, Little Rock.*

3:45 ***Patterns of Affect Expression in Infants with Nonorganic Failure to Thrive Syndrome (NFTT).** *D. K. Wilcox, H. Bauchner, and D. Frank. Division of Developmental and Behavioral Pediatrics, Boston (Mass) City Hospital, Boston University School of Medicine.*

4:00 ***Early Temperament and Cardiac Responses of Preterm (PT) Infants with Bronchopulmonary Dysplasia (BPD).** *C. G. Coll, B. M. Lester, M. Peucker, C. F. Z. Boukydis, and B. R. Vohr. Brown University, Women and Infants Hospital, Providence, RI.*

4:15 **Reducing Low Birthweight, Depression, and Stress Through Social Support in Pregnancy.** *A. W. Cross, K. J. Welshimer, E. Jackson, and J. Chapman. Center for Health Promotion Disease Prevention, University of North Carolina, Chapel Hill.*

4:30 ***Effects of Theophylline on Behavior in Children with Chronic Asthma.** *N. F. Slater, M. Green, H. Eigen, S. Hui, and H.G. Taylor. Indiana University School of Medicine, Departments of Pediatrics and Biostatistics, Indianapolis, and Case Western Reserve University, Cleveland, Ohio.*

4:45 **Evaluating a Parent Support Program for Mothers of Chronically Ill Children.** *H. T. Ireys, E. J. Silver, R. E. K. Stein, K. Bencivenga, and C. Koeber. Pediatrics, Albert Einstein College of Medicine, Preventive Intervention Research Center, Bronx, NY.*

5:00 ***Hypnoanalgesia in Sickle Cell Anemia.** *C. J. Erickson. Department of Pediatrics, Babies Hospital, Columbia University College of Physicians and Surgeons, New York, NY.*

5:15 ***Immunologic Changes Occurring at Kindergarten Entry Predict Respiratory Illnesses Following the Loma Prieta Earthquake.** *W. T. Boyce, E. A. Chesterman, D. Wara, F. Cohen, S. Folkman, and N. Martin. Department of Pediatrics, University of California, San Francisco.*

5:30 ***Rapid Calming Effect of Intraoral Sucrose in Crying Newborns.** *R. G. Barr, V. Quek, S. Young, and T. Oberlander. Departments of Pediatrics and Psychiatry, McGill University, Montreal, Quebec, and Montreal Children's Hospital.*

5:45 **Can the Reliability of Mothers' Clinical Judgments be Predicted?** *P. McCarthy, D. Cicchetti, S. Sznajderman, B. Forsyth, M. Baron, H. Fink, N. Czarkowski, B. Bauchner, and K. Lustman-Findling. Department of Pediatrics, Yale University School of Medicine, New Haven, Conn.*

6:00 **Cognitive Dysfunction in Children with Post-Meningitic Deafness.** *D. Kelly, B. Kelly, M. Jones, S. Verhulst and S. Bell.*

6:15 ***The Preschool Rapid Screen.** *M. L. Suchoff, M. H. Lifschitz, G. S. Wilson, N. LaFevers, and W. D. Williamson. Department of Pediatrics, Baylor College of Medicine, Texas Children's Hospital, Houston.*

EPIDEMIOLOGY AND PREVENTIVE PEDIATRICS

Grand Salon C

Moderators: *Robert Haggerty, MD, Nigel Paneth, MD, MPH, and Steven Shelov, MD*

3:00 **Firearms: Family Attitudes and Household Safety Practices.** *C. C. Wiley and R. Casey. Division of General Pediatrics, Children's Hospital of Philadelphia (Pa).*

3:15 **Previous Injury as a Risk Factor for Youth Suicide.** *D. C. Grossman, R. W. Soderberg, and F. P. Rivara. Department of Pediatrics, University of Washington, Harborview Injury Prevention Center, Seattle.*

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*Abstract was published in the Program Issue of the American ediatric Society and the Society for *Pediatric Research*, Pediatric esearch, April 1991.

3:30 ***Parental Alcohol Consumption and Children's Injuries: Evidence from the 1988 National Health Interview Survey (NHIS).** *P. E. Bijur and M. Kurzon. Albert Einstein College of Medicine, Department of Pediatrics, Bronx, NY.*

3:45 ***Increased Susceptibility of Infants to Red Measles (Rubeola) in a Well Vaccinated Society.** *D. W. Spady, H. F. Pabst, R. Marusyk, L. Chui, and M. Carson. Departments* of Pediatrics and Medical Microbiology and Infectious Diseases, University of Alberta, Edmonton

4:00 ***Measles Antibody in Baltimore Children.** *J. C. King, S. Feigelman, E. M. Hirshorn, C. L. Luna, C. A. Loffredo, and R. Lichenstein. Department of Pediatrics, University of Maryland, University of Maryland Hospital, Baltimore.*

4:15 ***Waning Immunity and Mild Measles in School-Aged Children Who Received Measles Vaccine Before 1979.** *M. B. Edmonson, J. L. Berg, and J. P. Davis. University of Wisconsin, Department of Pediatrics, and Wisconsin Division of Health, Madison.*

4:30 ***Risk Factors for Invasive Haemophilus Influenza Type b Disease in Victoria, Australia.** *D. Clements, I. Guise, and G. Gilbert. Department of Pediatrics, Duke University Medicine Center, Durham, NC, and Department of Microbiology and Infectious Diseases, Royal Children's Hospital (RCH), Melbourne, Australia.*

4:45 ***Validation of the Case-Control Method of Assessing A Vaccine's Efficacy.** *E. D. Shapiro. Yale School of Medicine, New Haven, Conn.*

5:00 ***Cigarette Smoking and Sudden Infant Death Syndrome (SIDS): No Dose Response in Data From the United States.** *H. J. Hoffman, M. Malloy, and D. Peterson. Prevention Research, NICHD, NIH, Bethesda, Md, and School of Public Health, University of Washington, Seattle.*

5:15 ***Maternal Substance Use and Sudden Infant Death Syndrome (SIDS) in Offspring.** *S. R. Kandall, K. Damus, J. J. Gaines, and L. Habel. Mt Sinai School of Medicine, Department of Pediatrics, Beth Israel Medicine Center; New York City Department of Health; Medical and Health Research Association of New York City, Inc, New York.*

5:30 ***Paternal and Maternal Birth Weights and Subsequent Pregnancy Outcome.** *M. A. Klebanoff. NICHD, NIH, Bethesda, Md.*

5:45 ***Cumulative Incidence of Atopic Disorders in High Risk Infants Fed Whey Hydrolysate, Soy, and Conventional Cow Milk Formulas.** *R. K. Chandra and A. Hamed. Memorial University of Newfoundland, Janeway Child Health Centre, St John's, Newfoundland.*

6:00 **Effects of Screening Children for High Cholesterol.** *C. M. Lannon and J. A. Earp. Department of Pediatrics, School of Medicine, and Department of Health Education and Health Behavior, School of Public Health, University of North Carolina, Chapel Hill.*

6:15 **Access to Care for Poor and Nonpoor Children: Separate and Unequal?** *R. F. St Peter and P. W. Newacheck. Robert Wood Johnson Clinical Scholars Program, Department of Pediatrics and Institute for Health Policy Studies, University of California, San Francisco.*

GENERAL PEDIATRICS AND PEDIATRIC EDUCATION

Grand Ballroom D

Moderators: *Frederick H. Lovejoy, Jr, MD,*
Lucy Osborn, MD, and
Michael Weitzman, MD

3:00 ***Office Diagnosis of Neonatal Chlamydial Conjunctivitis: Use of Kodak Surecell®.** *M. R. Hammerschlag, M. Gelling, P. Roblin, W. Dumornay, and M. Worku. Department of Pediatrics, SUNY Health Science Center at Brooklyn (NY).*

3:15 ***Missed Opportunities for Vaccinations in Pediatric Practices and the Effect on Vaccination Status.** *P. G. Szilagyi, L. E. Rodewald, S. G. Humiston, R. F. Raubertas, K. J. Roghmann, and C. B. Hall. Department of Pediatrics, University of Rochester (NY) School of Medicine and Dentistry.*

3:30 ***Prevalence of Urinary Tract Infection (UTI) in Febrile Infants.** *A. Hoberman, H. Chao, D. M. Keller, R. Hickey, H.M. Davis, and D. Ellis. University of Pittsburgh (Pa), Children's Hospital of Pittsburgh, Department of Pediatrics.*

3:45 ***Outbreaks of Human Enteric Adenovirus Types 40 and 41 in Houston Day Care Centers (DCC).** *R. Van, M. L. O'Ryan, D. O. Matson, L. Jackson, and L.K. Pickering. University of Texas Medical School at Houston and Baylor College of Medicine, Houston.*

4:00 ***Toxic Changes in Neutrophils as a Test for Kawasaki Syndrome (KS).** *P. C. Rowe, A. Quinlan, and B. K. Luke. Departments of Pediatrics and Epidemiology, University of Ottawa School of Medicine, Children's Hospital of Eastern Ontario, Ottawa.*

4:15 **Has the Eighty Hour Week Lessened Stress Levels in PL-1 Residents?** *J. E. Berkelhamer and N. H. Pliskin. Departments of Pediatrics and Psychiatry, Wyler Children's Hospital, University of Chicago (Ill) Pritzker School of Medicine.*

4:30 **Diagnostic Trends in a Pediatric Primary Care Clinic.** *C. Calderon, G. Gonzalez, and M. Valcarcel. Pediatric Department, University of Puerto Rico Ciencias Medicas, San Juan, Puerto Rico.*

4:45 **Comparison of Interviewing Skills of Fourth Year Medical Students with Their Individual Performance as Second Year Medical Students.** *R.D. OlsenandB.Anderson. Department of Pediatrics, Mayo Clinic, Rochester, Minn.*

5:00 **Reduction of Morbidity in Asthmatic Children Given a Spacer Device.** *S. J. Cunningham and E. F. Crain. Department of Pediatrics, Albert Einstein College of Medicine, Division of Pediatric Ambulatory Care, Bronx (NY) Municipal Hospital Center.*

5:15 ***Conductive Hearing Loss at Age 4 Years in Children Who Were <32 Weeks of Gestational Age.** *S. J. Gross. Department of Pediatrics, SUNY Health Science Center, Syracuse, NY.*

5:30 ***Appropriateness of Hospitalization in a Canadian Pediatric Hospital.** *J. E. Glcor, N. Kissoon, and G. I. Joubert. Children's Hospital of Western Ontario, Victoria Hospital, London, Ontario.*

5:45 ***Erythrocyte Protoporphyrin (EP) in Screening for Lead Poisoning at Blood Lead Levels Below 25 mcg/dl.** *S. Rajkumar and V. Rajagopal. SUNY Health Science Center at Brooklyn, Brooklyn, NY.*

6:00 ***A Change in Dietary Fat Composition Improves Serum Cholesterol Values in 7 to 13 Month Old Infants.** *H. Kovanen, E. Jokinen, A. Myyrinmaa, P. Salo, T. Ronnemaa, J. Viikari, I. Valimaki, and O. Simell. Cardiorespiratory Research Unit and Departments of Medicine and Pediatrics, University of Turku, and Rehabilitation Research Center of the Social Insurance Institution, Turku, Finland.*

6:15 **An Assessment of Nutritional Status in Homeless Children.** *J. H. Gould, T. L. Pelham, and J. C. Weiss. Department of Pediatrics, Jefferson Medical College, Philadelphia, Pa.*

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*Abstract was published in the Program Issue of the American Pediatric Society and the Society for *Pediatric Research*, Pediatric Research, April 1991.

Wednesday, May 1, 1991

9 AM-NOON

CLINICAL ISSUES

Grand Ballroom C

Moderators: Paul McCarthy, MD, and
Robert Pantell, MD

9:00 **Double-blind, Cross-over Trial of Psyllium Fiber in Hypercholesterolemic Children.** *B. A. Dennison. Department of Pediatrics, Cornell University Medical College and The Rogosin Institute, New York, NY.*

9:15 **Bacteriology of Acute Otitis Media (AOM): A New Perspective.** *M. A. DelBeccaro, P. M. Mendelman, A. F. Inglis, M. A. Richardson, and C. Clausen. Departments of Pediatrics and Otolaryngology, University of Washington, Seattle.*

9:30 **Brush Culture Method for Diagnosing Tinea Capitis.** *T. W. Hubbard and J. M. de Triquet. Department of Pediatrics, Eastern Virginia Medical School, Norfolk.*

9:45 **Utility of Oxygen Saturation in Evaluating the Response to Treatment in Wheezing Infants.** *A. J. Alario, W. J. Lewander, P. H. Dennehy, R. Seifer, and A. L. Mansell. Department of Pediatrics, Rhode Island Hospital, Providence.*

10:00 **Initial Weight Loss and Return to Birth Weight Criteria for Breast-Fed Infants: Challenging the "Rules of Thumb."** *S. DeMarzo, J. Seacat, and M. Neifert. Lactation Program, Presbyterian/Saint Luke's Medical Center, Denver, Colo.*

10:15 **Appropriateness of Admissions to a Canadian Children's Hospital.** *K. R. Kowaleski and M. Li. Division of Emergency Medicine, Department of Pediatrics, Children's Hospital of Eastern Ontario, Ottawa.*

10:30 **Parental Time and Expenses for Diabetes Care.** *G. E. Dougherty, A. Schiffrin, and L. Ball. Departments of Pediatrics and Epidemiology and Biostatistics, McGill University, Montreal, Quebec.*

10:45 **Simethicone in the Treatment of Infant Colic.** *T. J. Metcalf, T. G. Irons, L. D. Sher, and P. C. Young. Willow Creek Pediatrics, Salt Lake City, East Carolina University, Greenville; Pennisula Allergy and Pediatrics, Rolling Mills Estate, Calif; and University of Vermont, Burlington.*

11:00 **Tympanic Membrane Thermometers: Caveat Emptor.** *M. Nypaver, E. Zieserl, B. Nachtsheim, and A. T. Davis. Department of General and Emergency Pediatrics, Children's Memorial Hospital, Chicago, Ill.*

11:15 **Over-the-Counter (OTC) Medication Use in Children with Colds—A Critical Appraisal.** *M. B. H. Smith and W. Feldman. Department of Pediatrics, University of Ottawa, Ontario.*

11:30 **Intermittent Versus Continuous Amoxicillin Prophylaxis for Infants and Children with Recurrent Otitis Media With Effusion.** *S. Berman, R. Nuss, R. Roark, C. Huber-Navin, K. Grose, and M. Herrera. Department of Pediatrics, University of Colorado Health Sciences Center, Denver.*

11:45 **Duration of Positive Streptococcal Throat Cultures After Initiation of Antibiotics.** *L. W. Snellman, H. J. Stang, J. M. Stang, D. R. Johnson, and E. L. Kaplan. Departments of Pediatrics, Group Health Inc, and University of Minnesota, White Bear Lake.*

DEVELOPMENTAL AND BEHAVIORAL PEDIATRICS

Grand Salon A

Moderators: John Pascoe, MD, MPH, and
Modena Wilson, MD, MPH

9:00 **School Outcomes of Children with Asthma.** *M. G. Fowler, R. Garg, and M. G. Davenport. Office of Analysis, National Center for Health Statistics, Hyattsville, Md, and Clinical Trials Branch, National Health, Lung, and Blood Institute.*

9:15 **Homage to a Clinical Observation: Empirical Support for Wessel's Definition of "Colic."** *R. G. Barr, A. Rotman, J. Yaremko, D. Leduc, T. E. Francoeur, J. Desilets, and R. DuBerger. Department of Pediatrics, McGill University and Montreal (Quebec) Children's Hospital, Montreal.*

9:30 **Preventing Disruptive Night Waking in Infancy: An Effective Primary Care Intervention.** *R. Adair, H. Bauchner, B. Philipp, S. Levenson, and B. Zuckerman. Department of Pediatrics, Boston (Mass) City Hospital, Boston University School of Medicine.*

9:45 **Identifying Sources of Discrepancy Between Pediatricians' Diagnoses and the Child Behavior Checklist.** *S. M. Horwitz, P. J. Leaf, J. M. Leventhal, B. W. C. Forsyth, and K. N. Speechley. Departments of Epidemiology and Public Health and Pediatrics, Yale University School of Medicine, New Haven, Conn.*

10:00 **Understanding the Development of Failure to Thrive in a Low Birth Weight, Preterm Cohort: A Prospective Study to Age Three.** *P. H. Casey, K. Kelleher, R. H. Bradley, M. Swanson, L. Whiteside, S. Pope, and K. Barrett. Department of Pediatrics, University of Arkansas for Medical Sciences, Little Rock.*

10:15 **The Mental Health of Children Placed With Relatives.** *H. Dubowitz, V. Tepper, S. Zuravin, and S. Feigelman. Department of Pediatrics, University of Maryland Medical School, Baltimore.*

10:30 **Child Rearing Practices and Nursing Caries.** *J. R. Serwint, R. Mungo, V. Negrete, M. Guzman, and B. M. Korsch. Departments of Pediatrics and Pediatric Dentistry, University of Southern California School of Medicine and Children's Hospital of Los Angeles.*

10:45 **Detecting Family Violence in the Context of Pediatric Continuity Care.** *L. S. Wissow, M. E. H. Wilson, and D. Roter. Johns Hopkins Medical Institutions, Baltimore, Md.*

11:00 **Depression and Role Satisfaction in Mothers of Toddlers.** *A. L. Olson and L. A. DiBrigida. Department of Maternal and Child Health, Dartmouth Medical School, Hanover, NH.*

11:15 **Maternal Attitudes as Predictors of Infant Feeding Decisions.** *C. I. Dungy, J. Christensen-Szalanski, M. Losch, and D. Russell. Department of Pediatrics, The University of Iowa, Iowa City.*

11:30 **The Feasibility and Utility of Psychosocial Screening in a Pediatric Clinic.** *K. J. Kemper. Department of Pediatrics, University of Washington, and Harborview Medical Center, Seattle.*

11:45 **Developmental Delay Among Homeless Children.** *B. P. Dreyer, C. D. Courtlandt, A. H. Fierman, A. Arbel, G. Benincasa, C. Squittieri, L. Palevsky, and N. Mann. Department of Pediatrics, New York (NY) University School of Medicine, NY.*

EMERGENCY MEDICINE AND CHILD ABUSE

Grand Salon B

Moderators: John Leventhal, MD, and
Stephen Ludwig, MD

9:00 **The Failure of Tympanic Thermometry to Detect Fever Accurately in a Pediatric Emergency Department (PED).** *C. Garabedian, R. Vinci, D. Dwyer, and H. Bauchner. Division of Pediatric Emergency Medicine, Department of Pediatrics, Boston (Mass) University School of Medicine, and Boston City Hospital.*

9:15 **Refinement of the Child Vulnerability Scale.** *B. W. C. Forsyth, P. J. Leaf, S. M. Horwitz, and J. M. Leventhal. Departments of Pediatrics and Epidemiology and Public Health, Yale University School of Medicine, New Haven, Conn.*

9:30 **Cocaine-Exposed Newborns in an Inner-City Community Hospital.** *A. Theodorou, T. Holtrop, J. Marshall, K. Meert, and A. Sarnaik. Children's Hospital of Michigan, Wayne State University, and Samaritan Health Center, Detroit, Mich.*

9:45 **Pediatric Emergency Medicine—State of the Art.** *D. J. Isaacman, R. B. Karasic, and H. W. Davis. Department of Pediatrics, University of Pittsburgh (Pa) School of Medicine.*

10:00 **Defervescence as a Guide to Resolution of Bacteremia**

in Ambulatory Children. *F. Agre and L. R. Prieto. Department of Pediatrics, College of Physicians and Surgeons, Columbia University, New York, NY.*

10:15 **Positive Effect of an Educational Intervention on Compliance With Universal Precautions in a Pediatric Emergency Department.** *L. R. Friedland, M. Joffe, and J. F. Wiley, II. Emergency Medicine, Section of General Pediatrics, St Christopher's Hospital for Children, Philadelphia, Pa.*

10:30 **Historical Correlates to Anogenital Trauma in 1,150 Suspected Child Sexual Abuse Victims.** *D. L. Kerns and M. L. Ritter. Department of Pediatrics, Santa Clara Valley Medical Center, San Jose, Calif.*

10:45 **Screening for Cocaine Intoxication in Children with Unexplained Seizures in the Emergency Department.** *S. E. Krug, R. D. Marble, D. L. Lubitz, and T. J. Long. Department of Pediatrics, Case Western Reserve University School of Medicine, Cleveland, Ohio.*

11:00 **The Value of Chest Radiographs in the Evaluation of Febrile Infants Less Than Two Years Old.** *J. A. Taylor, S. Roncevich, E. Kouri, C. Talarico, and R. Schneider. Departments of Pediatrics, Radiology, and Emergency Medicine, Carolinas Medical Center, Charlotte, NC.*

11:15 **A New Instrument to Improve the Ability of Non-Experts to Identify Infants at Risk of Subsequent Child Abuse or Neglect.** *D. H. K. Ihnat, J. M. Leventhal, D. V. Cicchetti, D. R. Wasserman, and J. P. Hamilton. Department of Pediatrics, Yale University School of Medicine, New Haven, Conn, and Yale-New Haven Hospital.*

11:30 **Maltreatment of Children Born to Cocaine Dependent Mothers.** *D. R. Wasserman and J. M. Leventhal. Department of Pediatrics, Yale University School of Medicine, New Haven, Conn.*

11:45 **Are Interdisciplinary Evaluations of Alleged Sexual Abuse Cases Necessary?** *P. K. Jaudes and M. Martone. La Rabida Children's Hospital and Department of Pediatrics, University of Chicago (Ill) Pritzker School of Medicine.*

GENERAL PEDIATRICS

Grand Salon C

Moderators: Thomas G. DeWitt, MD, and
Ruth T. Gross, MD

9:00 **Doctorhoppers: Myth or Reality?** *C. Gosselink, D. Brazdziunas, E. Ekwo, A. Kresheck, and M. Lehmann. Department of Pediatrics, University of Chicago (Ill)/La Rabida Children's Hospital and Research Center.*

9:15 **What Factors Predict School Absence in Children with Chronic Medical Conditions? A Controlled Population Based Study.** *F. C. Jarman and M. C. Starr. Department of Pediatrics, University of Massachusetts Medical Center, Worcester.*

9:30 **Comparison of Two Methods of Assessing Appropriateness of Admission.** *K. R. Kowaleski, P. Griffin, and M. Li. Department of Pediatrics, Children's Hospital of Eastern Ontario, Ottawa.*

9:45 **Validity, Bias, and "Overcall" in Interpreting Chest Radiographs in Young Febrile Children.** *M. S. Kramer, R. Roberts-Brauer, and R. Williams. Departments of Pediatrics and Epidemiology and Biostatistics, McGill University, Montreal, Quebec.*

10:00 **An Analysis of Mental Health Service Utilization by Children in Foster Care in California.** *N. Halfon, G. Berkowitz, and L. Klee. Center for the Vulnerable Child, Children's Hospital Oakland, Calif.*

10:15 **The Relation of Family Mobility to Children's Emotional and School Functioning.** *G. A. Simpson and M. G. Fowler. National Center for Health Statistics, Hyattsville, Md.*

10:30 **Biofeedback: Initial Success in Treating Recurrent Abdominal Pain.** *A. J. Rosenberg, and T. Whitehead. Department of Pediatrics, University of Kansas Medical Center, Kansas City.*

10:45 **Are School-Based Clinics Serving the High-Risk Student?** *J. W. Stout and C. R. Anderman. Departments of Pediatrics and Epidemiology, University of Washington, Seattle.*

11:00 **A Clinic-Based Intervention to Promote Literacy.** *R. D. Needlman, L. E. Fried, and B. S. Zuckerman. Division of Developmental and Behavioral Pediatrics, Boston (Mass) City Hospital.*

11:15 **A Critical Appraisal of the Quality of Pediatric Journal Articles that Evaluate Diagnostic Tests.** *A. S. Bates, P. X. Margolis, and A. E. Evans. Departments of Pediatrics and Medicine, University of North Carolina, Chapel Hill, and Indiana University, Indianapolis.*

11:30 **Educational Effectiveness of a Lead Poisoning Video.** *S. Melman, S. Schorr, R. Lempert, and M. Polansky. Department of Pediatrics, Hahnemann University Hospital, Philadelphia, Pa.*

11:45 **Impact of Shorter Working Hours on Pediatric Housestaff Training.** *A. Willenborg, S. Shelov, and D. Neuspiel. Department of Pediatrics, Albert Einstein College of Medicine, Bronx, NY.*

PREVENTION AND EPIDEMIOLOGY

Grand Salon D

Moderators: Katherine K. Christoffel, MD, MPH, and
Sandra Elvik, MSN, CPNP

9:00 **Immunization Opportunities Missed Among Urban Poor Children.** *K. M. McConnochie and K. J. Roghmann. Department of Pediatrics, Rochester (NY) General Hospital, University of Rochester.*

9:15 **Predictors of Parental Injury Prevention Behavior.** *D. F. Schwarz, C. B. Forrest, J. A. Grisso, C. G. Miles, and V. M. Wolfson. Department of Pediatrics and Clinical Epidemiology Unit, University of Pennsylvania School of Medicine, Philadelphia.*

9:30 **The Functional Impact of Asthma.** *J. M. Perrin, M. L. Weitzman, and S. L. Gortmaker. Children's Service, Massachusetts General Hospital, Boston; Harvard School of Public Health, Boston; and University of Rochester (NY) School of Medicine.*

9:45 **Avoidable Pediatric Hospital Use: A Comparison of Admitting Physician Judgement With Utilization Review.** *J. L. Soulen, A. K. Duggan, and C. DeAngelis. Department of Pediatrics, Johns Hopkins University, Baltimore (Md).*

10:00 **Lead Intoxication in Early Infancy.** *M. W. Shannon and J. W. Graef. Department of Pediatrics, Harvard Medical School, Department of Medicine, Children's Hospital, Boston, Mass.*

10:15 **Children's Household Exposure to Guns.** *Y. D. Senturia, A. M. Teuscher, and K. K. Christoffel. Pediatric Practice Research Group, Children's Memorial Hospital, Chicago, Ill.*

10:30 **Finding the Missing Data—A Statewide System for Injury Surveillance in the Pediatric Office Setting.** *J. K. Sanders, E. R. Waring, and J. R. Zanga. Division of General Pediatrics and Emergency Care, Children's Medical Center, Medical College of Virginia/Virginia Commonwealth University, Richmond.*

10:45 **Management of Childhood Lead Poisoning: A Survey.** *D. Glotzer and H. Bauchner. Department of Pediatrics, Boston (Mass) University School of Medicine and Boston City Hospital.*

11:00 **Who Needs the Lead (Pb) Mobilization Test (LMT)? Blood Pb as the Sole Determinant of Need for Treatment.** *M. E. Markowitz and J. F. Rosen. Department of Pediatrics, Albert Einstein College of Medicine and Montefiore Medical Center, Bronx, NY.*

11:15 **Can We Influence Parents Whose Preschooler Has Been Recently Poisoned to Take Preventive Precautions?** *A. D. Woolf, A. Saperstein, and S. Forjuoh. Department of Pediatrics, Harvard Medical School, Boston; Division of General Pediatrics, Children's Hospital, Boston; and Massachusetts Poison Control System, Boston.*

11:30 **Gender Difference in Health Care Utilization by Children Away from Parental Influence.** *M. C. J. Rudolf and A. J. Alario. Department of Pediatrics, Rhode Island Hospital, Brown University, Providence.*

11:45 **Barriers to Influenza Vaccination in Children with Asthma.** *P. G. Szilagyi, L. E. Rodewald, J. Savageau, L. M. Yoos, and C. B. Doane. Department of Pediatrics, University of Rochester (NY) School of Medicine and Dentistry.*

APA Debate

Wednesday, May 1, 1991
8:30 PM-10 PM
Grand Salon A

esolved: That professional societies should accept financial contributions from commercial enterprises.

Moderator: *Kathleen Nelson, MD, APA President Elect; Professor of Pediatrics; and Director, Division of General Pediatrics, Children's Hospital, Birmingham, Ala.*

ro Resolution: Larry Shapiro, MD, Professor of Pediatrics and Biological Chemistry, Harbor UCLA Medical Center, Torrance, Calif, and Carol Berkowitz, MD, APA President; Professor, Clinical Pediatrics, UCLA School of Medicine; and Acting Chair, Department of Pediatrics, Harbor UCLA Medical Center, Torrance, Calif

Con Resolution: Catherine De Angelis, MD, Associate Dean for Academic Affairs and Professor of Pediatrics, Johns Hopkins Medical Institute, Baltimore, Md, and Steven P. Shelov, MD, Director, Pediatric Education, Albert Einstein College of Medicine, Montefiore Medical Center, Bronx, NY

General Plenary Session

Thursday, May 2, 1991
8 AM-NOON
Grand Salon D

Moderator: Kathleen G. Nelson, MD

8:00 **Managed Care for New York Medicaid Children: Cost Analysis of Referred Services.** *T. D. Sullivan. Department of Pediatrics, SUNY at Buffalo (NY), The Children's Hospital of Buffalo.*

8:15 **The Efficacy of Non-Invasive In-Hospital and Outpatient Management of Febrile Infants: A Four Year Experience.** *M. D. Baker, L. M. Bell, and J. R. Avner. Divisions of General Pediatrics, Emergency Medicine, and Infectious Diseases, The Children's Hospital of Philadelphia (Pa).*

8:30 **Increased Growth Velocities in Children Living in Shelters.** *C. D. Courtlandt, A. H. Fierman, B. P. Dreyer, K. Hick, D. Arnold, E. Keating, and N. Mann. Department of Pediatrics, New York (NY) University School of Medicine.*

:45 **The Prediction of Preschool Behavior Problems from Temperament and Other Variables in Infancy.** *F. Oberklaid, A. Sanson, R. Redlow, and M. Prior. Department of Ambulatory Pediatrics, Royal Children's Hospital, Victoria, Australia.*

9:00 **Vaccine Storage Errors in Pediatric Practice: The Tip of an Iceberg?** *D. M. Bishai, S. Bhatt, L. T. Miller, and G. F. Hayden. Department of Pediatrics, Cedars-Sinai Medical Center, Los Angeles, Calif, and University of Virginia Health Sciences Center, Charlottesville.*

9:15 **Use of the Fentanyl Lollipop for Analgesia During Painful Procedures in Children.** *N. L. Schechter, S. J. Weisman, M. Rosenblum, P. L. Conard, B. Bernstein, C. Bartolotta, C. San Antonio, B. Shapiro, and D. Cohen. Departments of Pediatrics and Anesthesia, University of Connecticut Health Center, Farmington; St Francis Hospital and Medical Center, Hartford, Conn; and Children's Hospital at Philadelphia (Pa).*

9:30 DISTINGUISHED CAREER AWARD

INTERMISSION

10:00 PRESIDENT'S ADDRESS

10:30 **The CBC Revisited: A Bayesian Reappraisal.** *M. S. Kramer, S. M. Tange, E. G. Mills, and M. L. Bernstein. Departments of Pediatrics and of Epidemiology and Biostatistics, McGill University Faculty of Medicine, Montreal, Quebec.*

10:45 **Clinical Risk Index for Bacterial Meningitis Among Febrile Children.** *R. Lembo, D. Krowchuk, and P. McCarthy. Department of Pediatrics, Yale University, New Haven, Conn, and Department of Pediatrics, Case-Western Reserve University at MetroHealth Medical Center, Cleveland, Ohio.*

11 00 **Randomized Trial of Laxatives in the Treatment of Encopresis.** *T. Nolan, G. Debelle, F. Oberklaid, and C. Coffey. Department of Pediatrics and Ambulatory Pediatrics, University of Melbourne, Royal Children's Hospital, Melbourne, Australia.*

11:15 **Maternal Emotional State and Infant Behavior: Are They Related?** *A. R. Miller and R. G. Barr. Department of Pediatrics, Montreal (Quebec) Children's Hospital.*

11:30 **Perinatal Injuries: Why Families File Suit.** *G. B. Hickson, E. W. Clayton, P. B. Githens, and F. A. Sloan. Vanderbilt Institute for Public Policy Studies, Health Policy Center, Vanderbilt University, Nashville, Tenn.*

11:45 **Maltreatment of Young Children Born to Teenage Mothers: A Comparison Between the Late 1960's and the Early 1980's.** *C. S. Rude, J. M. Leventhal, S. M. Horwitz, and D. M. Stier. Departments of Pediatrics, Epidemiology, and Public Health, Yale University School of Medicine, New Haven, Conn.*

Annual Meeting
The American Pediatric Society and The Society For Pediatric Research

New Orleans Hilton Riverside & Towers
and Rivergate Convention Center

Monday, April 29	Tuesday, April 30	Wednesday, May 1	Thursday, May 2
	7:45 AM-10:15 AM Poster Session II*, Poster Symposia, Nos. 7-12 **7:45 AM-11 AM** APS/SPR/APA Commercial Exhibits	**8 AM-9:30 AM** SPR Plenary Session; SPR Presidential Address; Young Investigator Award; Richard D. Rowe Award; Medical Student, House Officer, and Fellow Awards	**8 AM-11:30 AM** Subspecialty Platform Sessions III
	10:30 AM-1 PM APS Plenary Session; APS Presidential Address; APS Presidential State-of-the-Art Symposium, *Maternal & Child Health: Global Perspectives*	**9:30 AM-12:30 PM** Poster Session III* **9:30 AM-1:30 PM** APS/SPR/APA Commercial Exhibits **10 AM-12:30 PM** Poster Symposia, Nos. 13-18	
		12:30 PM-1:45 PM APS Business Meeting	**11:30 AM-12:45 PM** SPR Business Meeting
3:30 PM-7 PM Poster Session I* **3:30 PM-8 PM** APS/SPR/APA Commercial Exhibits **4:30 PM-7 PM** Poster Symposia, Nos. 1-6 **7 PM-8 PM** APS/SPR Opening Reception	**2 PM-3 PM** APS Howland Award, Joseph W St Geme, Jr, Leadership Award **3 PM-6:30 PM** Subspecialty Platform Sessions I and concurrent Joint APS/SPR/APA Subspecialty Platform Sessions	**2 PM-4:30 PM** SPR Presidential State-of-the-Art Symposium, *The Medical Social Crisis in Child Health* **2 PM-5:30 PM** Subspecialty Platform Sessions II	**1:30 PM-5 PM** Subspecialty Platform Sessions IV

*Please see poster session schedule for author attendance times.

Society For Pediatric Research 1991 — Subspecialty Platform Session Schedule

TUESDAY, APRIL 30, 3:00 PM—6:30 PM

Adolescent Medicine *(Grand Ballroom C)*
Behavioral Pediatrics *(Grand Salon D)*
Developmental Pharmacology I *(Belle Chasse)*
Epidemiology and Preventative Pediatrics *(Grand Salon C)*
General Pediatrics & Pediatric Education *(Grand Ballroom D)*
Hematology & Oncology I *(Napoleon)*
Immunology I *(Versailles)*
Infectious Diseases I *(Grand Salon B)*
Metabolism & Diabetes I *(Grand Salon A)*
Neonatology I *(Grand Ballroom A/B)*
Nephrology I *(Marlborough Suite)*

WEDNESDAY, MAY 1, 2:00 PM—5:30 PM

Gastroenterology/Nutrition I *(Grand Salon A)*
Genetics I *(Grand Salon B)*
Metabolism & Diabetes II *(Grand Salon D)*
Neonatal Cardiology *(Belle Chasse)*
Neonatal Epidemiology & Follow Up *(Versailles)*
Neonatal Immunology & Hematology *(Napoleon)*
Nephrology II *(Marlborough Suite)*
Pulmonology I *(Grand Ballroom C)*

THURSDAY, MAY 2, 8:00 AM—11:30 AM

Cardiology I *(Napoleon)*
Developmental Biology I *(Versailles)*
Endocrinology I *(Grand Ballroom D)*
Genetics II *(Grand Salon C)*
Gastroenterology/Nutrition II *(Grand Salon A)*
Neurology *(Marlborough Suite)*
Infectious Diseases II *(Grand Salon B)*
Neonatology II *(Grand Ballroom A/B)*
Pulmonology II *(Grand Ballroom C)*

THURSDAY, MAY 2, 1:30 PM—5 PM

Cardiology II *(Napoleon)*
Critical Care *(Grand Salon A)*
Developmental Biology II *(Versailles)*
Developmental Pharmacology II *(Belle Chasse)*
Dysmorphology and Teratology *(Marlborough Suite)*
Endocrinology II *(Grand Ballroom D)*
Immunology II *(Grand Salon D)*
Neonatal Infectious Diseases *(Grand Salon C)*
Neonatal Nutrition & Metabolism *(Grand Ballroom C)*
Neonatal Pulmonology *(Grand Ballroom A/B)*
Hematology and Oncology II *(Grand Salon B)*

1991 APS/SPR/APA Exhibitors

EXHIBITING COMPANY	CITY, STATE	BOOTH NUMBER
Air-Shields Vickers	Hatoboro, Pa	302, 304, 401, 403
Airborne Life Support Systems	Austin, Tex	419
Allied Healthcare Products, Inc.	St. Louis, Mo	514
Ameda/Egdell	Cary, Ind	102
American Journal of Diseases of Children	New Orleans, La, and Chicago, Ill	707
Appleton & Lang	East Norwalk, Conn	203
Applied Biometrics, Inc.	Eden Prairie, Minn	519
Baby's Benefit, Inc.	Colorado Springs, Co	404
Baxter Hyland Division	Glendale, Calif	418
Bear Medical Systems, Inc.	Riverside, Calif	207
Bunnell Incorporated	Salt Lake City, Utah	717, 719
Burroughs Wellcome Company	Research Triangle Park, NC	610, 612, 709, 711
Carnation Nutritional Products	Washington, DC	319
CNS, Inc.	Eden Prairie, Minn	609
Contemporary Pediatrics	Montvale, NJ	211
Corometrics Medical Systems, Inc.	Wallingford, Conn	414, 416
Davol, Inc.	Cranston, RI	209
DeVILBISS Health Care, Inc.	Somerset, Pa	611
Eli Lilly Company	Indianapolis, Ind	606, 608
Encyclopaedia Britannica, Inc.	Chicago, Ill	505
Endocrine Sciences	Calabasas, Calif	405
Fiberoptic Medical Products, Inc.	Allentown, Pa	507
Flexco Medical Instruments AG	Hendon, London, United Kingdom	513
Fujisawa Pharmaceuticals Inc.	Deerfield, Ill	110
Genentech, Inc.	South San Francisco, Calif	410, 412

EXHIBITING COMPANY	CITY, STATE	BOOTH NUMBER
Gerber Products Company	Fremont, Mich	508
Hemocue, Inc.	Mission Viej, Calif	502
Hewlett-Packard Company	Waltham, Mass	213, 215
Hologic, Inc.	Waltham, Mass	618, 620
ICN Pharmaceuticals	Costa Mesa, Calif	617, 619
Infrasonics, Inc.	San Diego, Calif	703
Infusaid, Inc.	Norwood, Mass	206
Intelligent Medical Systems	Carlsbad, Calif	104
International Technidyne Corporation	Edison, NJ	518
J.B. Lippincott Company	Philadelphia, Pa	307
John Wiley & Sons, Inc.	New York, NY	713
La Leche League International	Franklin Park, Ill	420
Lederle Laboratories	Wayne, NJ	614
Mallinckrodt Medical, Inc.	St. Louis, Mo	503
Marquette Electronics	Milwaukee, Wis	317
Mead Johnson Nutritionals	Evansville, Ind	306, 308
MED MARK, Inc.	Olathe, Kan	517
MEDELA, Inc.	Crystal Lake, Ill	520
Medfusion, Inc.	Duluth, Ga	201
Medical Associated Services, Inc.	Hatfield, Pa	615
Medical Data Systems	Wayne, Pa	406, 408
Medical Research Center	New York, NY	512
Merck, Sharp, & Dohme	West Point, Pa	705
Mosby-Year Book, Inc.	St. Louis, Mo	218
N.I.C.H.D.	Bethesda, Md	511
National Center for Health Statistics	Hyattsville, Md	112
Natus Medical Inc.	Foster City, Calif	407
Neonatal Intensive Care	Santa Monica, Calif	305
Nichols Institute	San Juan Capistrano, Calif	118
Non-Invasive Monitoring System, Inc.	Miami, Fla	504
NTI/White River	Laguna Hills, Calif	120
Nurticia-Loma Linda Foods	Riverside, Calif	318
Ohmeda	Madison, Wis	602, 604
Physicians Engineered Products	Park Rapids, Minn	320
Plenum Publishing Corporation	New York, NY	605
Preemicare Corporation	Houston, Tex	106, 108
Promedica, Inc.	Burlingame, Calif	616
Ross Laboratories	Columbus, Ohio	402
Sandoz Pharmaceuticals Corp.	East Hanover, NJ	301, 303
Scale Tronix, Inc.	White Plains, NY	613
Schering-Plough Corporation	Kenilworth, NJ	603
Sechrist Industries	Anaheim, Calif	607
Serono Laboratories, Inc.	Norwell, Mass	202
Sigma Tau Pharmaceuticals	New York, NY	506
SmithKline Beecham Pharmaceuticals	Philadelphia, Pa	205, 208
Social Security Administration	Baltimore, Md	515
SpaceLabs, Inc.	Redmond, Wash	217
Springer-Verlag NY Publishers	New York, NY	501
The Langer Biomechanics Group, Inc.	Deer Park, NY	715
Thermoscan, Inc.	San Diego, Calif	417
W.B. Saunders Company	Philadelphia, Pa	601
Western Reserve Care Systems	Youngstown, Ohio	509
Williams & Wilkins	Baltimore, Md	510
Wyeth Pediatrics	Philadelphia, Pa	701
Zila Pharmaceuticals, Inc.	Phoenix, Ariz	114

Annual Meeting of the Ambulatory Pediatric Association

GENERAL POSTER SESSION
Monday, April 29, 3:30 PM-7 PM

Poster No. 147
Direct Bilirubin Measurements in Jaundiced Term Newborns: A Waste of Blood and Money?

T. B. Newman, S. Hope, and D. K. Stevenson

General Pediatrics and Epidemiology,
University of California, San Francisco,
and Stanford (Calif) University

Most authorities recommend measurement of direct bilirubin as an initial step in the evaluation of jaundiced newborns. However, true conjugated hyperbilirubinemia is rare, and measurements of direct bilirubin are often inaccurate, suggesting that the predictive value of a high direct bilirubin value might be low. To investigate this possibility, we used a computerized database and medical records to review the outcome of 5255 measurements of direct bilirubin on 2877 term newborns in two hospitals. Test ordering frequency and results varied markedly between the two institutions: direct bilirubins were ordered about 10 times more often at the University of California, San Francisco than at Stanford, and the reported results were more than twice as high. One hundred forty-nine babies had maximum direct bilirubin values in the top 5% for their hospital of birth. In most, the high direct bilirubin remained unexplained (52%) or was due to laboratory error (21%). Forty infants (27%) had possibly associated conditions. These conditions were identified as a result of elevation of direct bilirubin in only four, all of whom had minor laboratory abnormalities which resolved spontaneously. Thus, none of the 5255 measurements of direct bilirubin in this study was clearly useful. Because of the low yield of unsuspected treatable pathology and very poor specificity, measurement of direct bilirubin is a poor screening test. More selective ordering of direct bilirubin tests could lead to considerable cost savings without an adverse effect on health.

Poster No. 148
Home Phototherapy—Use and Attitudes Among Community Pediatricians

S. B. Meropol, A. A. Luberti, A. R. De Jong, and J. C. Weiss

Department of Pediatrics,
Jefferson Medical College, Philadelphia, Pa

Despite almost 20 years of published experience with the use of home phototherapy (HP) for the treatment of neonatal unconjugated hyperbilirubinemia, many pediatricians still admit such patients to the hospital. This study investigates the fears and experiences of pediatricians related to the use of HP.

A questionnaire was sent to 139 pediatric practices in the Philadelphia area. Of the 93 responders, (67% response rate), only 30 (32%) had used HP. Similarly, of the 10 non-responders who were contacted by telephone, only 30% had used HP.

Twenty-two users (81%) had less than a 10% failure rate with HP. Twenty-four users (89%) stated that more than 75% of parents were satisfied with HP. While 25 (41%) of the non-users had worries about parental non-compliance with eyeshields and with phototherapy itself, only 1 (4%) of the users actually had major problems in each of these areas. Although 23 (38%) of the non-users reported a fear of medico-legal consequences as a reason for non-use, none of the practitioners using HP had ever been threatened with a potential lawsuit stemming from its use. Eighteen (30%) of the non-users feared overheating and dehydration, but none of the users experienced major difficulties with these problems.

Some of the perceived fears of non-users actually were confirmed as major problems by the users: parental anxiety (non-users 28% vs. users 24%); and difficulty obtaining home blood testing (non-users 26% vs. users 17%). Also, 17% of the users experienced major difficulties with insurance reimbursement.

This study reveals that the use of home phototherapy is still limited in this region despite favorable reviews in the literature and positive experiences of local practitioners. There is a substantial discordance between the disadvantages of HP feared by non-users and the problems actually experienced by those who utilize this home treatment. Providing education and better ancillary support services supports may allow more practitioners to feel comfortable using this method of treatment.

No. 149
The Health Status of Children Placed With Relatives

H Dubowitz, S. Feigelman, S. Zuravin, V. Tepper, R. Lichenstein, and N. Davidson

Department of Pediatrics,
University of Maryland Medical School, Baltimore

Placement with relatives is generally the first option of public agencies seeking substitute care for children, mostly due to child abuse or neglect. This is the first evaluation of the health care, prevalence of chronic health problems, and need for further treatment of children placed in this type of foster care.

METHOD: Subjects were *all* 524 children living in relative placements in Baltimore in April 1989. Data were gathered from medical records, mailed questionnaires to health care providers, parents, relative caretakers, caseworkers and the adolescents, and by a history and physical exam.

RESULTS: Primary care was clearly received by about 25% of the children, with uncertainty accounting for another 66% of the children. About 50% were adequately immunized; most of the remainder had uncertain status. Over 40% of the children had not seen a dentist in the prior year. The salient medical findings included poor vision (10%), poor hearing (eg, 9% of 6-11 year olds), failure to thrive (10% of 0-5 year olds), obesity (20% of teens), dental caries (22%) and asthma (18%). Only 10% of the children had no medical problem; 52% had 1-2 problems and the remainder had >2 diagnoses. Many of the problems had not been previously identified, evaluated or treated. Over half the children had ≥1 health problem that definitely needed follow-up.

Few background variables predicted the number of health problems. However, children with more health problems were more likely to have a caretaker who made frequent contact with the caseworker ($p = .04$), was unemployed ($p = .004$), and who received more services ($p = .009$). Children who were older at placement ($p = .001$), and had less educated caretakers ($p = .04$) who were noncompliant with keeping appointments ($p = .04$) had a greater number of *untreated* health problems.

IMPLICATIONS: Children placed with relatives appear to have substantial health care needs. However, their problems are similar to those of poor and other foster children. Nevertheless, greater responsivity to their needs by families, health professionals and the social service system is indicated.

Poster No. 150

Foster Children: Predictors of Developmental Problems on Baseline Health Assessment

S. M. Horwitz and M. D. Simms

Department of Epidemiology and Public Health,
Yale University, New Haven, Conn, and
Foster Care Clinic, St Mary's Hospital, Waterbury, Conn

We know little about the rate or predictors of developmental problems for children entering foster care. We investigated these issues in a cohort of 272 children who received a unique baseline medical/developmental assessment in the Foster Care Clinic (FCC), St. Mary's Hospital, Waterbury, CT, from 6/85 to 12/89. Children ranged in age from 1 mo. to 7.8 yrs. at initial assessment, 57% were male, 39% were caucasian, 31% African-American, 20% Hispanic, and had been in foster care an average of 7 months at assessment. Reasons for placement included 15% abuse, 49% neglect, and 36% at risk for abuse/neglect. Significant growth stunting was noted in 19.5% and wasting in 8.4%. Children were assessed with the Battelle Developmental Inventory (BDI). Fifty-three percent ($N = 144$) of children scored ≤10th% in at least one area of development, with 39% ($N = 106$) of children impaired in ≥2 areas.

Factors related to developmental problems included: older age (>1 year) at first foster placement ($RR = 1.8$, $p = .01$); placement for abuse/neglect rather than "at risk" status ($RR = 1.6$, $p = .02$); and less time in foster care prior to the assessment ($RR = 2.0$, $p = .000$). Using these three variables, we constructed 2 risk categories: in the high risk category, 87% (39/45) had ≥2 developmental problems; in the moderate risk category, 32% (56/176) had multiple developmental problems. High risk children were: older at entry into care, placed for abuse/neglect, and had been in care <3 months at baseline assessment.

We conclude that many children entering foster care have developmental problems and that problems are highly prevalent in a particular subgroup of children. Given the importance of early intervention, it is critical that all children entering substitute care receive a complete evaluation and, further, that particular attention be paid to older children who are placed for abuse/neglect.

Poster No. 151

Measurement of Gestational Cocaine Exposure

C. M. Callahan, T. M. Grant, P. Phipps, G. D. Clark, A. H. Novack, A. P. Streissguth, and V. A. Raisys

University of Washington, Seattle

Studies of fetal cocaine exposure have challenged the validity of maternal drug history and recommended analysis of infant biologic specimens. We studied the relationships between history of maternal drug use, radioimmunoassay (RIA) of trimester specific segments of maternal hair, meconium, newborn urine and hair. We hypothesized that meconium and newborn hair would prove most sensitive.

We studied 60 postpartum women who delivered a live newborn between 11/89 and 12/90. Subjects were eligible if they completed an anonymous questionnaire and a confidential interview. Meconium was analyzed by fluorescence polarization immunoassay and gas chromatography/mass spectrometry (GCMS).

Maternal history for cocaine use and RIA of maternal hair correlated (kappa statistic = 0.95). The sensitivities of newborn biologic specimens were assessed by McNemars Test for Correlated Proportions-Exact Method. Multiple regression analysis was used to evaluate the relationship between the quantity of cocaine found in the newborn hair with the amount detected in the trimester specific maternal hair segments.

RIA of newborn hair and GCMS of meconium were more sensitive than immunoassay of urine ($P < 0.05$).

The quantity of benzoylecgonine found in the newborn hair correlated best with that detected in the segment of maternal hair representing the third trimester ($R = 0.66$, 95% C.I. $0.48 < R < 0.79$).

Analysis of either newborn hair by RIA or meconium by GCMS are more sensitive than immunoassay of urine in determining gestational cocaine exposure. Drugs detected in newborn hair correlate with the maternal pattern of use during the third trimester.

Immunoassay of urine to detect gestational cocaine exposure is not sensitive. Newborn hair or meconium is more sensitive and can detect most third trimester fetal cocaine exposure.

Poster No. 152

Effects of Head Start on Children With Lead Poisoning

B. Howard and E. Charney

Department of Pediatrics,
Duke University Medical Center, Durham, NC,
and Department of Pediatrics,
University of Massachusetts Medical Center, Worcester

Children with lead poisoning are at high risk for poor developmental outcome from the CNS toxicity of lead and also from poor nutrition including Fe deficiency and suboptimal parenting. We attempted to improve their outcome with a combined program: a small group Head Start class 5½ days/week plus parenting-nutrition sessions for their mothers. A prior pilot study demonstrated developmental gains in the children and suggested that the parent group program was key to its success. This study involved 36 low-income black children 30-54 months with Class II/III lead poisoning (PbB 25-50 ug/dl) and their mothers, enrolled in both child and parent groups for one school year; 31 matched controls attended regular Head Start with no parent groups. After one year there were no between group differences. However, both groups had significant verbal IQ gains (3.3) and improved HOME environment scores (4.0). HOME scores improved whether or not the mothers attended the parenting sessions. Drops in PbB (3.2 ug/dl) and FEP (6.6 ug/dl) were significant and comparable in both groups. IQ correlated negatively with PbB but also with maternal depression (CES-D), # of social problems and negative parenting attitudes (PSI). Behavior problems (CBCL) correlated with social factors (CES-D, PSI, HOME, # social problems, life stress) and iron deficiency but not with PbB (all $p < .05$). This study indicates that gains in Head Start may relate to its effect on parents, not well studied previously. The study also suggests that the neurobehavioral effects attributed to lead are also significantly related to family dysfunction and iron deficiency. We conclude that lead poisoned children can particularly benefit from Head Start with its effects on both parent and child.

Poster No. 153

Elevated Lead (Pb) Levels in Abused Children

W. Bithoney, W. Barbaresi, A. Vandeven, and A. Ryan

Department of Medicine,
Children's Hospital, Boston, Mass

To test our hypothesis that abused children are at increased risk for lead (Pb) poisoning we measured whole blood Pb levels in 95 children who had reports of physical abuse made by clinicians in our primary care clinic (PCC) and a comparison group of 95 children from the PCC without symptoms of abuse. All parents completed a demographic and housing questionnaire. Comparison subjects were matched to cases on age, race, SES and housing type. All cases were identified prospectively over a 48 month period. Cases were ascertained in all seasons.

During the study periods 74% of eligible case children had lead levels determined. Abused children had Pb levels of 17±4.25 µgm/dl SEM. Comparison subjects Pb was 11±3.82, p<.001 by paired t-test. Abused children were more frequently anemic, a possible Pb effect, had higher FEP levels, p<.001, and had significantly more peeling paint in their homes, p<.04. 19% of abused children had Pb levels so high as to require chelation while only 4% of comparison subjects had Pb levels this high. Many authors have suggested that lead levels formerly thought to be inconsequential are toxic. Clinicians caring for abused children must attend to a broad range of concerns, thus, all abused children, known to be epidemiologically at risk for Pb elevation, should have Pb levels drawn. Correction of iron deficiency and elevated Pb may result in improved developmental outcome in these children.

Poster No. 154
Getting Away With Murder?: A Study of Unintentional Child Shootings

J. T. Maurer, M. J. Barthel, and R. R. Tanz

Department of Pediatrics, Children's Memorial Hospital,
Northwestern University Medical School, Chicago, Ill

Is anyone held accountable when children are shot unintentionally, i.e. without intent for anyone to be injured, or are such shootings considered just the cost of gun ownership in our society?

Using a database of children <17 years old treated at our hospital for gun injuries from 1980-1990, we identified children shot unintentionally. Police data available since 1984 were then linked to medical and court records to determine the identity of the shooter, the weapon used, the legal charges filed and the legal outcome in each case. Police officers were interviewed whenever possible. Involvement of child protective services (CPS) was determined. From 1/84-3/90, 19/78 (24%) children were shot unintentionally. 13/19 (68%) shootings involved handguns. 4/19 (21%) victims died, 7 (37%) suffered neurologic impairment. Most victims were male (68%) and nonwhite (53%). 11 (58%) victims were <10 years old. Shooters were older: 15 (79%) ≥10 years old; 18/19 were male. 95% of the gun owners were related to the victim or the shooter. At least 11 state and local laws covered the shootings. Police interviewed were ambivalent about filing charges in these cases. Charges were filed against the shooter in 4/19 (21%) cases; 2 were convicted. Gun owners were charged in 8 (42%) cases; 3 were convicted. Fines totalled $150 and no one was imprisoned. Hospital social services became involved in 10 cases; 5 were reported to state CPS with 1 finding of neglect.

CONCLUSIONS: 1) Handguns were the predominant weapon used in these unintentional shootings; 2) Shooters and gun owners were rarely held accountable for the injuries caused; 3) The state child protection agency was rarely involved; 4) Making gun owners and shooters responsible for unintentional shootings of children will require a shift in attitudes throughout our society.

Poster No. 155
Patterns of Causation for Intentional Injury in a Population Based Study of Urban Children

L. L. Davidson, M. S. Durkin, P. O'Connor,
B. Barlow, and M.C. Heagarty

Departments of Pediatrics,
Pediatric Surgery, and Public Health,
Columbia University, New York, NY,
and Russell Sage College, Troy, NY

Although the proportion of intentional injuries causing death to urban children is rising, little is known of the pattern of injury causation which does not result in death. The denominator in this epidemiological study of injuries was an urban population of 91,000 children under 17. The numerator was drawn from three sources covering a five year period: the medical records of the two primary hospitals serving the area and the deaths certificates from the Department of Health. This represents 100% of the deaths and a sample of 77% of the hospitalizations.

Of the 2752 injuries causing hospitalization or death, almost 9% were intentional. Of the 76 deaths to children, 34% were intentional. This varied by age in a J shaped distribution rising sharply in adolescence: 4% of the 841 injuries to 1-4 year olds were intentional, while 12% of the 685 to 10-14 year olds and 25% of the 353 to 15 and 16 year olds were intentional assaults. The patterns of specific causes were also related to the age of the children.

Proportion of Intentional Injuries Due to Specific Causes

Causes(%):	Striking	Falls	Drown	Burns	Guns	Pierce	Ingest	Undetermined*
Age Groups(N)**								
<1 yr(17)	35	18	6	6	0	0	0	35
1-4 yr(30)	27	3	0	17	7	0	7	37
5-9 yr(38)	68	3	0	3	13	3	0	3
10-14 yr(83)	52	5	0	0	16	22	0	5
15-16 yr(88)	36	4	0	0	32	25	0	1

*This category includes what seemed to be primarily striking injuries, but the history was not clear enough to assign an E-code

**N = number of intentional injuries

What can be concluded is that drowning, ingestions and burns are primarily found as intentional injuries only in the younger age groups while gun shot wounds and stab/piercing injuries occur with increasing frequency in the older age groups. Given that the underdetermined category seem to be primarily striking injuries, striking as a cause of intentional injury occurs across the age range.

Poster No. 156
Physician Decisions to Report and Label Suspected Child Maltreatment

L. S. Wissow, M. E. H. Wilson, and G. L. Zellman

Department of Pediatrics, Johns Hopkins University
School of Medicine, Baltimore, Md,
and The Rand Corp, Santa Monica, Calif

Despite legal requirements many physicians do not report all cases in which they suspect maltreatment. This study examined how differences in specialty, attitudes, and experience influence the decisions of primary care physicians to make reports and label cases as abuse or neglect. Subjects were a random sample of Maryland pediatricians, family practitioners, and emergency physicians (n = 727). Mailed questionnaires asked for anonymous responses to vignettes of 3 cases of injury said to be related to a small child's accidental household fall. Variations in the cases allowed separate measurement of the effects of caretaker identity (mother or stepfather) and injury type (head contusion, skull or femur fracture). For each case physicians were asked if they would report suspected maltreatment and if the report would be for abuse or neglect. They were also asked for opinions on 8 statements about the impact of reporting (the chance of resolving the problem alone, the risk of losing the family, etc.). There were 351 questionnaires returned (48%); differences in response rate by specialty and rural/urban residence were considered in the calculation of results, as were variations in the vignettes' portrayal of injury severity and caretaker.

The specialties differed in practice setting, prior experience with maltreatment, and attitudes about the effects of reporting. Family practitioners were most likely to be working in direct contact, continuity settings. They were least likely to have ever reported child abuse (76% vs. more than 90% for pediatricians and emergency physicians). Emergency physicians were most likely to support prompt reporting; family practitioners tended to endorse a more cautious approach. Attitudes about reporting were more important determinants of intention to report the study vignettes than was specialty. On average, less cautious physicians were 40% more likely to say they would report study cases than were physicians who were more cautious. Physicians endorsing a cautious approach to reporting were more likely to label the cases they intended to report as neglect rather than abuse. We conclude that differences in physician attitudes about reporting may contribute to inconsistencies in the application of reporting laws and the responses of agencies whose actions vary by the type of report received.

Poster No. 157

Sexual Abuse by Father-Figures: A Comparison of Natural Fathers, Stepfathers, and Mothers' Paramours

A. R. De Jong

Department of Pediatrics, Jefferson Medical College of Thomas Jefferson University, Philadelphia, Pa

Sexually abused children often name father-figures as abusers. Although increased abuse risk has been suggested within stepfamilies, little has been written comparing abuse by stepfathers (SF), natural fathers (NF), and mothers' paramours (MP). The purpose of this study was to compare specific features of the abuse and the childrens' responses to abuse by NF, SF, and MP.

All victims under age 15 years seen at a sexual assault center were included in the descriptive data and behavioral assessments were obtained on all keeping followup appointments. Father-figures were abusers in 308 cases (NF = 128, SF = 65, MP = 115), representing 23.3% of all child victims. No significant variation was found among the three father-figure groups with respect to the victims' age or gender, type of sexual contact, presence of physical trauma, whether violence was involved, whether followup appointments were kept, or the frequency of phobias, sleep problems, regression, somatic complaints or behavior changes in their victims. (Chi square, $p > .05$)

Stepwise regression analysis was performed using the abuser group as the dependent variable. The analysis included 14 sociodemographic variables, abuse descriptors, and childrens' responses which were significant or approached significance. Only four variables were predictors of the abuser group: duration of abuse ($p < .01$, $R^2 = .068$), child expressed anger ($p < .01$, $R^2 = .101$), race ($p < .01$, $R^2 = .145$), and child expressed guilt ($p < .01$, $R^2 = .175$). NF often abused children for >1 year (34%). Victims verbalized more guilt (19%) and less anger (27%). SF also often abused children for >1 year (42%). Victims verbalized average guilt (12%), but more anger (45%). MP rarely abused victims for > 1 year (8%), and abuse was more often disclosed after a single episode than NF or SF abuse (32% vs 18%). Their victims rarely expressed guilt (0%), but frequently expressed anger (47%). A higher percentage of NF abusers were white (NF = 41%, SF = 18%, MP = 15%).

Despite many similarities in specific features of abuse by NF, SF, and MP, significant differences in abuse dynamics are reflected in the victims' responses and expressed feelings.

Poster No. 158

An Association Between Sexual Abuse and Early Adolescent Pregnancy

J. E. Cox, L. Coyne, and W. G. Bithoney

Department of Pediatrics, Harvard Medical School, and Childrens Hospital, Boston, Mass

We examined the hypothesis that a history of sexual abuse predisposes adolescents to early parenthood. The medical records, which included detailed interviews, of 147 inner-city, welfare dependent adolescent mothers, aged 13-17 years, followed in a hospital based teen tot clinic were examined for history of sexual abuse and age of first pregnancy. The population was 76% black, 22% hispanic, and 2% white. 28 (19.3%) of young mothers had history of sexual abuse prior to their first pregnancy. 16 of the 34 perpetrators (47.1%) were family members. Only 8/34 episodes (23.5%) were immediately disclosed with 9 (26.5%) revealed more than one year later. Of the 28 mothers with history of sexual abuse, 19 were abused prior to age 12 (67.8%) and 9 (32.2%) after age 12 with an average age of first abuse of 9.7 years. 9/19 (47.4%) of the episodes prior to age 12 years involved intercourse compared to 7/9 (77.8%) of episodes after age 12 years ($p < 0.05$). 11 of the 28 mothers with history of sexual abuse received psychotherapy.

These 28 teen mothers were compared to the 119 teen mothers without past history of sexual abuse. The mothers with history of sexual abuse were younger at first pregnancy with a mean age of 15.0 ± 1.4 years than those without history of sexual abuse who first became pregnant at 16.3 ± 1.3 years ($p < 0.005$). Mothers with history of sexual abuse were more likely to have been in foster care, 14/28 (50%) vs. 23/119 (19.3%), ($p < 0.005$), and to have used illicit drugs, 7/28 (25%) vs. 10/119 (8.4%), ($p < 0.01$). Since our study was based on a record review, it probably underestimates the extent of sexual abuse in our population. However, our study demonstrates that history of sexual abuse is common in adolescent mothers. More importantly, adolescents with a history of sexual abuse become parents at an earlier age than do adolescents without a prior history of sexual abuse. Further studies are needed to examine both the background of sexual abuse in our population and the sequelae of sexual abuse.

Poster No. 159

Utilization of Prenatal Care by Adolescents: Who Starts When?

M. C. Pew, J. M. Leventhal, and S. M. Horwitz

Department of Pediatrics,
Yale University School of Medicine, New Haven, Conn

Early prenatal care has been associated with better outcomes for teenage mothers and their children, yet only half of teenage mothers begin care early. The purpose of this study was to assess whether adolescents delay because of 1) limited access to care or 2) characteristics of the teens themselves. We surveyed 57 primigravida women ≤ 18 yrs. of age (mean age: 16 yrs.), who sought care in a hospital-based program for inner-city young mothers from 1/90-8/90. With a semi-structured interview and review of the medical records, we collected information about barriers to care and personal and social details. Teens who enrolled early (in the first trimester) were compared to late enrollees.

Thirty of the 57 teens (53%) enrolled early, and 27 (47%) enrolled late. There were no differences between early vs. late enrollees in age, race, grade in school, method of payment, waiting time for the appointment or transportation time to the clinic. In contrast, the early enrollees were more likely to have a telephone (97% vs. 74%; $p < .002$), and to seek other medical care before pregnancy (50% vs. 18%; $p < .02$). While both groups suspected pregnancy early, the early enrollees shared the news sooner (1.9 mo. vs. 2.9 mo.; $p < .002$), were more likely to tell only family at first (27% vs. 0%; $p < .005$), and less likely to plan to move after delivery (20% vs. 48%; $p < .03$). Depression was twice as frequent among late enrollees (52% vs. 26%; $p = .05$).

In summary, young teenagers who began prenatal care late had the same access to care as those who began early, but their socioeconomic status, health behaviors, reliance on family and prevalence of depression were different. We conclude that the tendency to delay prenatal care accompanies important risk factors for a poor outcome of pregnancy, such as extreme poverty and depression. Improving the outcomes of teenage pregnancies will require more than increasing access to prenatal care.

Poster No. 160

Adolescent Aids Education in a Pediatric Emergency Department

A. J. Behrman, K. N. Shaw, and F. S. Shofer

Departments of Internal Medicine and Pediatrics,
University of Pennsylvania School of Medicine,
Philadelphia

Two-hundred and seventy-eight subjects aged 12-25 from an inner-city pediatric emergency department (ED) serving a minority population were surveyed for AIDS-related knowledge, attitudes, and risk behavior as they waited for care for themselves or their children. Subjects completed a 61-question survey followed by a short videotape or no educational intervention. Both groups were re-interviewed by telephone at 1-2 weeks. There were no significant differences between the groups for age, gender, parental status, baseline knowledge or follow-up rates. Twenty-nine percent admitted risk factors for HIV infection.

Analysis showed that over 90% knew HIV transmission could occur via sex, intravenous drug abuse (IVDA), contaminated blood products, and perinatal transmission. However, there were striking deficiencies in baseline knowledge. For example, many believed that AIDS was transmitted via toilets (26%), eating utensils (39%), coughing (29%), blood donation (28%), and mosquitos (54%); blood transfusion was considered a high risk by 54%. A high percentage did not know that AIDS could be acquired from anal sex (26%), oral sex (40%), or sex with a healthy IVDA (21%); nor that other sexually transmitted diseases (STDs) increased the risk of HIV infection (75%). Seventy percent did not know AIDS is increasing among black women. Only 56% remembered ever hearing about AIDS in school (despite a well established K-12 public school AIDS program). There were no differences in baseline knowledge scores with respect to age, gender, or admitted risk behavior. Follow-up knowledge scores were better overall for the intervention group than the controls ($p<0.05$). Specifically, scores were significantly improved in the intervention group with respect to the risk of anal sex, oral sex, and coexisting STDs; the increase in AIDS among black women; and knowing where to get further information.

High risk adolescents and young adults seeking non-acute care in inner city EDs may lack access to other sources of AIDS education. The ED waiting room can be a site for effective educational intervention.

Poster No. 161

Clinical Utility of Chlamydia Trachomatis Diagnostic Techniques in Adolescent Women

F. M. Biro, S. F. Reising, and J. A. Doughman

Department of Pediatrics,
Children's Hospital Medical Center,
University of Cincinnati, Ohio

To evaluate the clinical utility of various diagnostic tests, 2 enzyme immunoassays (Abbott Chlamydiazyme (CZM), Syva Microtrak (MT), and a non-isotopic DNA probe (Gen-Probe Pace II (GPP) were compared to cell culture (with monoclonal antibody confirmation) for the diagnosis of endocervical *Chlamydia trachomatis* infection. There were 479 consecutive patients enrolled, of whom 473 had complete data collection. The order of sample collection was randomized. Patients were stratified according to whether they were asymptomatic (N=206), symptomatic (defined by patient's symptoms of dysuria, discharge, burning, or abdominal pain) (N=219), or test of cure (N=48). Discrepant analysis was performed when culture was negative and nonculture technique was positive. The patient was considered to have *C. trachomatis* if culture was positive, or if 2 or more alternate techniques were positive. Overall prevalence of *C. trachomatis* was 11.7% in the asymptomatic, 23.2% in the symptomatic, and 6.2% in the test of cure group. Because there were few positive Chlamydia results in the test of cure group (4 of 48), no further analyses were performed. Sensitivity (SENS), specificity (SPEC), positive predictive value (PPV), and negative predictive value (NPV) were calculated for both symptomatic and asymptomatic groups. Pending discrepant analysis for GPP, the following results were obtained:

	Symptomatic				Asymptomatic			
	SENS	SPEC	PPV	NPV	SENS	SPEC	PPV	NPV
Culture	72.5	100	100	92.3	79.2	100	100	97.3
CZM	72.5	100	100	92.3	50.0	100	100	93.8
MT	86.3	98.8	95.7	96.0	79.2	98.9	90.5	97.3
GPP	70.6	95.8	83.7	91.4	70.8	95.6	68.0	96.1

Clinical presentation should influence the choice of test(s) for a specific patient.

Poster No. 162

Peer Screeners to Identify Substance Abuse in Pregnant Teens

S. Barnett, D.P. McCormick, G. Wilkinson, and A. Berensen

Departments of Pediatrics,
Preventive Medicine/Community Health, and Obstetrics,
University of Texas Medical Branch at Galveston

Despite the growing recognition of disastrous outcomes in pregnant adolescents using drugs and alcohol, the early diagnosis of this problem remains elusive. In a meta analysis of prevention studies Tobler reported improved results using peer-oriented drug prevention programs.

We compared two methods of screening adolescents for drug use. First, a peer screener (PS), a 16 year old Hispanic female, used a structured interview beginning with innocuous questions and progressing to queries regarding substance use in pregnant/post partum teens. Second, during a routine prenatal exam, obstetrical practitioners (OBP), female physicians' assistants with 5-9 years of experience, queried pregnant teens about cigarette, alcohol, and drug use. IRB approved oral assent obtained by the PS; confidentiality was maintained. Results are:

No. of Patients	Peer Screeners n=69 % #	OB Practitioners n=41 % #	Relative Risk
Any Substance Use	65.0(45)	27.0(11)	2.41
Smoking	18.7(13)	19.5(8)	0.96
Alcohol	33.2(23)	12.2(5)	2.72
Drugs	37.7(26)	19.4(8)	1.94

The two groups were similar in age, race, and socio-economic mix. The PS was 2.41 times more likely to identify a history of positive substance use than the OBP. Similar findings occurred in identifying alcohol (2.72) and drug (1.94) use but not tobacco use (0.96).

A peer screener may be more likely to identify substance use in pregnant teens. Controlled studies to evaluate these findings are planned to determine whether peers on clinical health teams could improve diagnosis of substance use in pregnant adolescents.

Poster No. 163

PID: Evaluation and Treatment in a Pediatric vs Adult Emergency Department

J. M. Lavelle, I. Reyes, and K. N. Shaw

Department of Pediatrics, University of Pennsylvania
School of Medicine, Philadelphia;
The Children's Hospital of Philadelphia;
and The Hospital of the University of Pennsylvania,
Philadelphia

A one year retrospective study of 399 adolescent females who presented to an adult (194) or pediatric (205) emergency department and evaluated for PID was conducted. Race, socioeconomic status, presenting complaints, rate of positive GC cultures, severity of illness as determined by objective clinical and laboratory criteria, and treatment rate at first visit were similar at both institutions. Although charts from both institutions lacked important documentation, information was more likely to be lacking from the pediatric charts; gravity was not recorded in 86% as compared to 18% at the adult ED, and results of pregnancy testing were unknown in 24 pediatric ED patients vs. 7 adult ED patients. At both institutions RPR results were unknown in 30% of cases, of those done, 12% were reactive. Ultrasounds were done in 22% pediatric patients vs. 4% adult patients with similar rates of positive results.

Adolescents diagnosed with PID were more likely to be admitted if they presented to a pediatric ED, [odds 2.5 (95% CI: 1.3-5), $p<0.005$] even when physical exam findings were absent; 18% had no cervical motion tenderness, 20% had no adnexal tenderness, and 43% had no lower abdominal tenderness. However, no patient was admitted to the adult hospital without these findings. When only patients who met objective criteria for PID were compared, the adolescent at the pediatric hospital was still more likely to be admitted, [odds 4.4 (95% CI: 1.8-11), $p<0.001$], especially those under 16 years of age ($p<0.02$).

Many adolescent patients are seeking care for PID in pediatric settings, therefore education and standard of care need to be improved. These data are also reflective of conflicting policies regarding hospitalization of young females for PID.

Poster No. 164

Prior Advice Seeking and Increased Appropriate Use of a Paediatric Emergency Room

T. F. Oberlander, I. B. Pless, G. E. Dougherty, and D. McGillivray

Department of Pediatrics,
McGill University, Montreal, Quebec

Seeking advice prior to an unscheduled visit to a pediatric emergency room (PER) may influence the appropriate use of this setting for minor illnesses. To address this issue a questionnaire was given to parents of children 0-18 years ($n=489$) visiting a PER, asking whether they had sought advice from family, friends, or a physician and about factors possibly related to the decision to seek care. Appropriateness was rated, blind to discharge diagnosis, by two pediatricians using an established algorithm incorporating child's age, time of visit, clinical state and problem at presentation. Substantial agreement was found between these pediatricians (Kappa = .71). The response rate was 50% and non-responders did not differ significantly with respect to age, sex, time of visit and appropriateness rating. Overall, 34% of visits were appropriate.

Bivariate analysis showed appropriateness was significantly related to advice seeking, having a regular physician, two or more children, older parents and the absence of prior treatment ($p<.05$); it was not related to sex, time since last physician visit or level of parents' education ($p>.05$).

A logistic regression model with appropriateness (Yes/No) as outcome showed appropriate visits occurred significantly more often when a parent spoke to both a physician and non-physician prior to visiting the PER, than when only one of these individuals was consulted, or when no advice was sought (Odds Ratio [OR] 2.7, 95% confidence interval [CI] 1.4-5.3). [Talking to a physician alone, OR 1.7, CI 1.0-2.8; talking to a non-physician alone, OR 1.6, CI .9-2.9]. The model also showed that having a regular physician and two or more children contributed significantly (OR 2.2, CI 1.1-4.3; OR 2.1, CI 1.3-3.1, respectively).

These findings suggest that appropriate use of a PER is positively influenced by prior advice seeking, especially with a physician and family member, having a regular physician and a parent's past child care experience.

Poster No. 165

Prehospital IV Placement in Children

K. A. Grisanti and D. M. Jaffe

Department of Pediatrics, Hospital for Sick Children,
University of Toronto (Ontario)

Sick and injured children present unique challenges in diagnosis, psychosocial care, and successful accomplishment of essential procedures to prehospital care providers. Our purpose was to examine the ability of a unified metropolitan paramedic system with no intraosseous protocol to provide intravenous (IV) access when indicated. All paramedic transports involving children in metropolitan Toronto from January, 1988 through October, 1990 were reviewed. Indications for IV access, rates of successful placement, and time to achieve access were determined. Age related failure rates were compared using the chi-square statistic and time to achieve IV access using the t-test.

There were 477 children < 19 years, comprising 4.7% of all paramedic transports. The mean age was 9.0 years. 40% were < 6 years, and 61% were male. The paramedic diagnoses were: trauma (31%); seizures (27%); asthma (13%); cardiac arrest (5%); and respiratory distress (5%). Condition during transport included 34% with decreased level of consciousness, 9% with seizures, and 8% with vital signs absent (VSA).

IV attempts were made in 277 children (58%). IV placement was obtained in 236 (85% of patients attempted). The mean time from arrival on scene to IV placement was 9.8 minutes (range 1-45 minutes). Our strict criteria for IV placement were: cardiac arrest, shock, extensive burns, major trauma, and intubation. Of the 152 children who met criteria, 29% failed to receive an IV. IV placement was not attempted or unsuccessful in 47% of children < 6 years meeting criteria, as compared to 22% in children $\geqslant 6$ years ($p = .003$). Non-trauma patients accounted for most of the age related difference. Of children < 6 years with VSA, the failure rate was 63% but only 23% in children $\geqslant 6$ years ($p = .026$). Time to achieve successful access did not differ among age groups.

We conclude that skilled paramedics are unable to achieve IV access when indicated in a significant proportion of children especially those < 6 years of age. Intraosseous access may provide a useful alternative.

Poster No. 166

Responses of Children, Parents, and Nurses to Tympanic Thermometry in the Pediatric Office

D. T. Alexander and B. A. Kelly

Department of Pediatrics,
University of Pennsylvania
School of Medicine, Philadelphia,
and Children's Hospital of Philadelphia

This study was designed to assess children's behavioral responses to tympanic thermometry. In addition, parents' and nurses' impressions of this new technology were evaluated. Infrared tympanic thermometry eliminates the risks associated with traditional methods of temperature taking including mucus membrane contact and glass breakage. Temperature taking by this method is rapid taking only one second. 224 patients were enrolled from three private pediatric practices in suburban Philadelphia during regular office hours. Patients were alternately assigned to have their temperature taken with either a tympanic thermometer or with a rectal or oral thermometer depending on the patient's age. Parents and nurses were then asked to fill out a short questionnaire to describe their observations of the child's behavior during temperature taking and to describe their own feelings about the temperature taking method used. Parents were also asked to assess their usual method of temperature taking at home and their child's usual behavioral response at home.

Tympanic thermometry was rated higher by both parents and nurses for speed, ease, cleanliness, and safety. These differences were statistically significant. Parents and nurses were more confident in the accuracy of traditional temperature taking methods. Children whose temperatures were taken rectally were more likely to be observed by both parents ($p=.02$) and nurses ($p=.01$) to have a negative behavioral reaction to the procedure than children whose temperatures were taken by tympanic thermometry. There was no difference observed between the behavioral responses of children who had temperatures taken orally and those who had tympanic thermometry.

Our data show that the benefits of tympanic thermometry are appreciated by both parents and nursing professionals. Temperature taking can be particularly upsetting for the younger child. The data from this study clearly suggest that young children prefer tympanic thermometry to rectal temperature taking.

Poster No. 167

Effect of Personalized Letter Reminders on Preventive Appointment Show Rates and Vaccination Status

I. R. Campbell, P. G. Szilagyi, L. E. Rodewald, C. B. Doane, and K. J. Roghmann

Department of Pediatrics, University of Rochester (NY), Strong Memorial Hospital

Postcard reminders specifying the time of preventive health care (PHC) visits improve show rates in primary care settings. Few studies have evaluated personalized letter reminders that specify the content of an upcoming PHC visit (e.g., immunizations, anticipatory guidance). While personalized reminders are costly to create, they can inform parents of the benefits of an upcoming PHC visit. We studied the effect of personalized letter reminders (L), generic postcard reminders (P) or no reminders control; C) on PHC visits of infants enrolled at a teaching hospital pediatric continuity clinic.

In this prospective clinical trial, newborns (N = 295) were randomized to one of the three study groups and followed for 13 months. The clinic staff were blind to group allocation. For every PHC visit the investigators sent either postcards to the P group or letters specific to the particular PHC visit to the L group.

There were no differences in demographic features among the groups (Table). The show rates for the L and P groups were not different from each other, and were significantly higher than the show rate for the control group. The L and P groups had fewer appointments scheduled per patient, but the number of kept appointments per patient was the same for all groups. The mean age of completion of the primary DPT series was the same for the groups.

We conclude that (1) costly personalized letter reminders, while providing more information to parents, are no more effective than inexpensive postcard reminders in this setting, 2) vaccination status is not improved by either type of reminder in a setting having high immunization rates for infants, and 3) letter and postcard reminders improve clinic efficiency by dereasing the number of unused, scheduled appointments.

	Percent Medicaid[2]	2-Factor Hollingshead[3]	PHC SR[4]	# Sched Visits	# Kept Visits	Age at 3rd DPT
Letter[1]	89	57	73.1%*	5.9*	4.2	7.6 mo.
Postcard[1]	78	55	74.4%*	6.0*	4.3	7.0 mo.
Control	83	58	67.6%	6.7	4.3	7.6 mo.

Group compared with control group (t-test) * $P < 0.05$ [2]Chi-square mong all groups = 3.87, P = 0.2 [3]Hollingshead score, based on head f household occupation and education [4] Show rate (SR)

Poster No. 168

Metal Detectors—An Alternative Approach to he Evaluation of Coin Ingestions in Children?

. P. Ros and F. Cetta

ediatrics, Loyola University Medical Center, Maywood, Ill

Foreign body ingestions constitute a common problem in peiatric emergency medicine. Recent data indicate that, despite urrent recommendations, most children who ingest coins do not ndergo radiologic evaluation. The purpose of this study was to etermine the accuracy of a metal detector in localizing coins in model simulating coin ingestions in children. The distance beween the anterior chest wall (ACW) and the esophagus was measured on seventeen chest computed tomograms obtained on hildren between the ages of three months and six years. Subequently, a diameter equal to the mean ACW to lower esophgeal sphincter measurement was marked across the investigaor's forearm. A second investigator then attempted to detect the resence of the coin through the forearm by using a Super Scaner (Garrett Security Systems Inc, Texas) metal detector. The tudy was conducted in a blinded manner and consisted of fifty ttempts equally divided between pennies, nickels, dimes, quarters and controls (no coin). The accuracy of the metal detector in identifying the presence or absence of coins in our model was 100%. We conclude that the metal detector evaluated by us is highly accurate in identifying coins through human tissues and it should become a valuable and practical tool in the evaluation of children following a coin ingestion.

Poster No. 169

Efficacy of Cough Suppressants in Treating Nighttime Cough in Children

J. A. Taylor, A. H. Novack, J. R. Almquist, and J. E. Rogers

Department of Pediatrics,
University of Washington, Seattle,
and Carolinas Medical Center, Charlotte, NC

Data are not available on the efficacy of cough suppressants in pediatrics patients with acute cough. To test our hypothesis that guaifenesin with codeine (C) or with dextromethorphan (DM) are effective in alleviating the symptoms of nighttime cough a double-blinded, placebo-controlled study was conducted. Children 18 months-12 years old with significant nighttime cough were recruited from private pediatric practices. Parents responded to a questionnaire describing the severity of 3 symptoms (amount of coughing, loss of sleep, and post-tussive emesis) on the previous night for use as baseline data for each patient. The child was then randomized to receive C, DM or placebo (PL) at bedtime for 3 consecutive days with completion of an identical questionnaire rating the symptoms each night. Answers were transformed to an ordinal scale for analysis. A successful therapeutic intervention was defined as a reduction of at least 2 points in cough score on any day of the study from cough score at baseline (range 0-4 for each day). A composite symptom score was computed for each day (range 0-10); reduction in symptom score was calculated by subtracting symptom score for any day of study from symptom score at baseline. Of 49 eligible children 13 received PL, 19 DM, and 17 C. On entry mean cough and symptom scores were similar for each group ($P > 0.2$). Percent of patients with a successful therapeutic intervention, and mean reduction in symptom score for each drug for each day are summarized below.

	% of Patients With Successful Therapy			Mean Reduction in Symptom Score		
	day 1	day 2	day 3	day 1	day 2	day 3
PL	46.2	46.2	76.9	2.67	3.62	4.69
DM	57.9	47.4	63.2	2.95	3.28	4.13
C	29.4	64.7	82.4	1.76	2.47	3.85

For every comparison between study drugs the P value was > 0.05; the smallest P value was 0.10 comparing reduction in symptom score on day 1 between DM and C. We conclude that there is little difference between PL, DM and C. Cough suppressants are not indicated for treatment of nighttime cough in children.

Poster No. 170

Milder Symptoms Occur in Recurrent Episodes of Streptococcal Infection

K. A. Woodin, L. H. Lee, and M. E. Pichichero

Department of Pediatrics, University of Rochester, NY

We hypothesized that Group A streptococcal (GABHS) recurrences with homologous serotypes present with milder symptoms than those encountered on initial infection.

Data collected prospectively as part of a multi-centered, randomized antibiotic efficacy trial performed during 1981-1983 was re-evaluated to answer this question. Patients were routinely evaluated at 4-6 days, 18-21 days and 32-35 days following the start of treatment or if they were symptomatic. All casebooks were reviewed and patients with second infections in which M typing or T agglutination data and anti-streptolysin O and anti-DNAase serology was available were evaluated. Recurrences were defined as the presence of the same serotype on follow-up ulture with evidence of antibody rise. Charts from all eligible atients were abstracted for signs and symptoms of GABHS inection. The data was analysed with the Student t test and chiquare analysis; each recurrent infection was compared with the nitial infection.

Seventy (24%) of the 295 patients had a second episode of ABHS infection during the study period. Twenty-eight recurences were identified; they occurred a mean of 23 days following he initial infection (median 21 days). These patients showed significant differences between their two infections for symptoms f sore throat, headache, chills (p<.001), and signs of fever p=.003), pharyngeal erythema (p<.001), exudate (p=.007), alatal petechiae (p=.01), and ≥2+ adenitis (p=.004). However, arache, upper respiratory tract symptoms, stomache, tonsillar nlargement, and scarletina were similar on both occasions.

Milder symptoms occur with recurrent homologous GABHS nfections compared with the initial infection. These findings are elevant since patients with milder symptoms may be less likely seek physician attention.

oster No. 171

trategies for Diagnosis (Dx) and Treatment of ebrile Infants: Clinical and Cost-effectiveness

. A. Lieu, M. N. Baskin, J. S. Schwartz, and G. R. Fleisher

epartment of Pediatrics,
niversity of Pennsylvania, Philadelphia

Fever in infants may signify serious bacterial infection. We conucted a clinical and cost-effectiveness analysis for Dx and Rx of fants 29-89 days with T≥38.0 C. The baseline analysis used data n 503 pts in a study of intramuscular ceftriaxone (IM cef) and stimates from the literature to evaluate 6 strategies: (1) No Dx, o Rx; (2) Lumbar puncture (LP) with CSF, blood (Bcx), and rine (Urcx) cultures, white blood count (WBC) and urinalysis A), + intravenous antibiotics (IV abx) for all pts; (3) LP + IM f for all pts with nl LPs; (4) Bcx & Urcx with WBC and UA; (5) BC & UA; (6) Judgment. In strategies 4, 5, and 6, pts judged high risk had Rx with IV abx; low-risk pts were observed as utpts without abx. For a hypothetical cohort of 100,000 febrile fants, the results are:

	# of Deaths or major sequelae	# (%) of sequelae prevented	# of abx compls/ sequelae prevented	Avg cost/ pt	Cost/death or sequelae prevented
LP + IV abx	244	747 (75)	34	$2038	$272,600
LP + IM cef	248	743 (75)	23	528	71,000
Bcx & Urcx	398	594 (60)	14	846	142,500
WBC & UA	468	523 (58)	16	841	160,800
Judgment	692	299 (30)	30	823	275,300
No Dx, No Rx	991	0 (00)	NA	247	NA

Sensitivity analyses show that the choice of strategy depends eatly on the effectiveness of im cef and the sensitivity of the BC & UA. WBC & UA prevents more sequelae than LP + IM f only when IM cef is assumed to be less than 53% effective. e conclude that: (1) strategies which combine LP and abx for pts prevent the most sequelae; (2) LP + IM cef has equal clinical d superior cost-effectiveness compared with LP + IV abx; strategies which use WBC & UA or clinical judgment do not rpass strategies which use LP + abx even when test sensitivity very high.

ster No. 172

ood Cultures in the Outpatient Setting: hat Is the Optimum Number & Method?

J. DiPasquale, G. G. Gaar, and A. B. Anderson

e Emergency Associates for Medicine,
e Tampa (Fla) General Hospital

btaining blood cultures (BC's) in young children to rule out teremia without contaminating the specimen has always been a challenge in the outpatient setting. Pediatricians traditionally obtain one BC while in the adult population multiple cultures are routinely obtained. The optimum number of cultures and method of collection for pediatric patients remain to be determined. This study was designed to analyze 1) the sensitivity of one versus two BC's and 2) the difference in contamination rates between collection methods.

In this prospective clinical study, all patients 0-18 years of age who met predetermined criteria to have a BC drawn were eligible. 408 patients were enrolled from August to November, 1990, representing 6.6% of total patient visits to the Pediatric Emergency Care Center at Tampa General Hospital. Two sets of BC's were obtained from each patient using a standard protocol employing aseptic technique. The first set was collected through a newly inserted IV catheter. The second set was collected at a separate venipuncture site using a butterfly or straight needle exclusively for collection of the BC specimen. A minimum blood volume of 0.5 ml was obtained for each bottle. Cultures were separated by an interval of at least 10 minutes. A standard data collection sheet was completed on each patient. All cultures were processed in the clinical microbiology lab. Followup was done by chart review and or telephone contact. Data analysis was done using the sign test.

To date, true pathogens were identified in 11/408 (2.7%) BC's. All 11 pathogens were identified in the first set of BC's, while only 8/11 (73%) cultures were also positive in the second set. Analysis of contaminants shows that 38/408 (9.3%) of the first specimen were contaminated versus 7/408 (1.7%) from the second specimen ($p < .01$).

At the present time our data do not allow us to draw a statistical conclusion concerning the necessity of more than one BC. Further data from this ongoing study will be presented at the time of the meetings. It is clear that obtaining BC's through newly inserted IV catheters significantly increases the risk of contamination ($p < .01$). The ideal method for obtaining BC's appears to be phlebotomy for the sole purpose of obtaining a specimen for culture.

Poster No. 173

Diagnostic Test Ordering in the Evaluation of Febrile Children: the Role of Physician and Environmental Factors

D. L. McGillivray, R. Roberts-Brauer, and M. S. Kramer

Departments of Pediatrics and Epidemiology
and Biostatistics, McGill University, Montreal, Quebec

Patient factors such as age, temperature, duration of illness, and "toxicity" are known to affect physicians' use of diagnostic tests in febrile children. Our objective was to assess the independent effects of physician (gender, practice type, and experience of attending staff; presence and level of trainees) and environmental (pre- or post-July 1, patient load, time of day, day of week, referral status) factors on ordering a complete blood count, blood culture, BUN, urinalysis, urine culture, throat culture, chest x-ray, and lumbar puncture. We prospectively studied 6,191 consecutive visits by nonadmitted febrile (rectal T ≥38.0°C) children <18 years of age to a children's hospital emergency department from March 1989 to November 1989. Multiple logistic regression analysis was used to control for the mutually confounding effects of patient, physician, and environmental factors and to assess attending staff-trainee interactions (effect modification).

One or more diagnostic tests were ordered in 39.6% of the visits. Patients evaluated by hospital-based subspecialists were more likely to receive tests than those evaluated by community-based physicians [e.g., odds ratio (OR) for complete blood count = 1.28 (95% confidence interval = 1.12-1.46)]. Children seen by physicians with >10 years experience were significantly less likely to receive tests than those seen by their more junior colleagues, but this effect was modified substantially by trainee presence and level. For example, when no trainee was involved, care by experienced physicians had an OR (relative to care by those with <5 years experience) of 0.51 (0.38-0.68) for ordering a chest x-ray. Involvement by a junior trainee (medical student, intern, or first-year resident), however, increased the OR to 0.79 (0.59-

..07), while involvement by a senior resident increased the OR o 0.96 (0.72-1.29). For all tests except the throat culture, patients ieen on or after July 1 were significantly more likely to be tested e.g., OR = 1.36 (1.16-1.58) for blood culture]. These attending itaff, trainee, and seasonal effects on test ordering have important implications for febrile children and their families, clinical raining and supervision, and health care costs.

’oster No. 174

lanagement of Febrile Infants y Practicing Pediatricians

). Bergman, R. Pantell, S. Brotherton,
nd the PROS Network of the AAP

)epartment of Pediatrics,
Jniversity of California, San Francisco

The optimal management of febrile infants remains elusive. ecause of the low incidence of serious illness (bacterial menigitis and sepsis) for which errors in clinical judgment are of onsiderable consequence, adequate sample sizes of febrile inants have not been achieved making studies of clinical predictors nconvincing.

The Pediatric Research in Office Settings (PROS) Network of he American Academy of Pediatrics has completed two separate wo month pilot studies (n = 200, n = 120) of febrile (>38.0°C) inants (<2 months). Two hundred and thirty-eight physicians in 1 practices from 33 states provided prospective observational ata on their diagnostic and management approaches to febrile nfants seen in their offices. This group of infants were predomnantly white (82.2%) and only 15.7% received Medicaid or were ithout insurance. Sixty-nine percent of infants did not appear l and 10% had no further laboratory evaluation. Screening labratory tests were commonly performed with 90% obtaining VBC, 77% blood cultures, 74% urinalysis, 69% urine culture and 4% lumbar puncture. Twenty one percent of infants did not eceive antibiotics and 34% of infants were sent home. Of those nfants hospitalized 52% had a specific illness diagnosed or susected, while 48% were hospitalized as part of the physicians' outine management. The incidence of bacterial meningitis (1%) nd sepsis (3%) in these studies from office practice are similar reports from hospital-based series, and too small to make eaningful statements about the accuracy of clinical predictors. lso clinically noteworthy was urinary tract infection being dignosed in 8% of the total sample (11% of infants with urinalysis).

In conclusion, this study documents the considerable variation diagnostic and management approaches to febrile infants by large national sample of practicing pediatricians. This practice ariability and the capacity of a nationwide collaborative network rovides an opportunity to complete the large scale (n>3000) utcome study required to determine the accuracy of different inical strategies in detecting serious illness.

oster No. 175

he Value of Early Treatment for the revention of Lyme Disease

. Agre and R. M. Schwartz

epartment of Pediatrics,
ollege of Physicians and Surgeons,
olumbia University, New York, NY

Over a three year period 179 patients were enrolled in a double lind, placebo controlled early treatment program for the preention of Lyme disease. Enrollment criteria were that the paent be age 3 to 19 years of age and that the deer tick bite occurred o more than three days prior to treatment. The tick was brought the physician for identification or identified by the family after oking at preserved specimens or pictures. Acute and six week onvalescent blood samples were drawn for Lyme titer rise. Seological testing was done by I.F.A. 89 patients were randomized treatment with penicillin or tetracycline, 250 mgm Q.I.D. for days and 90 patients to placebo. Of four patients with weekly ositive titer rise, one patient had clinical Lyme disease that received placebo. Of the remaining 3 patients with weekly positive titer rise, all of whom received a placebo, 1 had a Flu-like illness and 2 had no symptoms. No patients receiving an antibiotic had a significant titer rise. In a two and half year follow-up, no patient developed stage 2 or 3 Lyme disease. We conclude that because of the low incidence of Lyme disease in children bitten by a deer tick early prophylactic treatment is not warranted.

Poster No. 176

Adaptive Behavior in Subgroups of Children With Attention Deficit Disorder and Hyperactivity Disorder (ADHD)

N. J. Roizen, T. A. Blondis, and M. Stein

Department of Pediatrics,
University of Chicago (Ill)
Pritzker School of Medicine,
and Wyler Children's Hospital, Chicago

Children with ADHD often have impaired social competence. To better describe and quantitate this, the scores on the Vineland Adaptive Behavioral Scales (1984) (Vineland) which measure personal and social sufficiency were compared to Wechsler Intelligence Scale for Children-Revised (WISC-R) scores in children with ADHD. The subjects consisted of 74 children diagnosed in the multidisciplinary Hyperactivity and Learning Problem Clinic as having ADHD based on a combination of history, clinical observation, and standardized IQ tests, achievement tests, and behavior rating scales. The children with ADHD were separated into3 subgroups: ADHD (n = 31), ADHD plus a learning disorder (LDADHD, n = 21), and ADHD plus oppositional defiant disorder. (ODDADHD, n = 22). The following was found:

	ADHD	LDADHD	ODDADHD
WISC-R Verbal IQ	99.0(SD±19.0)	98.4(SD±14.7)	99.6(SD±15.3)
WISC-R Performance IQ	97.9(SD±15.5)	96.8(SD±20.9)	100.7(SD±13.7)
WISC-R Full Scale IQ	97.8(SD±16.0)	97.0(SD±17.9)	100.4(SD±14.1)
Vineland Communication SS	82.0(SD±12.8)	70.7(SD±13.3)	71.3(SD±14.3)
Vineland Socialization SS	87.7(SD±17.2)	84.0(SD±17.9)	72.0(SD±14.3)
Vineland 3 Factor SS	79.7(SD±12.9)	73.1(SD±14.2)	68.6(SD±11.9)

Results indicated significant discrepancies between IQ and Vineland functions for all subgroups ($p \leq 0.04$). When all subgroups are combined and comparisons between WISC-R and Vineland scores are made the results show dramatic significance ($F = 136$, $p \leq 0.00001$). This study demonstrates that ADHD children with average intelligence show major adaptive dysfunction which is greater if the ADHD is associated with LD or ODD.

Poster No. 177

Who Provides Health Care to the Children of Physicians?

L. Dusdieker, J. Murph, C. Dungy, and W. Murph

Department of Pediatrics, University of Iowa
Hospitals and Clinics, Iowa City

To define health care interventions performed by physicians for their own children, a Likert scale questionnaire was sent to 701 physicians (residents, fellows and faculty) at a large midwestern teaching hospital. Of the 492 respondents 353 were parents of children ≤ 18 yrs of age. The father was identified as the parent physician (PP) in 78% of cases, the mother in 5% and both mother and father in 16%. A non-family physician was listed as the child's MD by 96% of the respondents. The majority of PP reported treating their afebrile child for acute illnesses such as vomiting, diarrhea, colds, etc. In this situation, 36% of PP rarely or never contacted the child's primary doctor. However, if the ill child was febrile (≥38.5°C), 55% of PP rarely or never treated without consultation. Only 47% of PP always performed a physical exam of the ill child prior to treatment. Physicians were most likely to auscultate the chest of a child with a cough or examine the tympanic membranes of a child with ear pain and least likely to obtain a clean catch urine in a child with dysuria or a throat swab from a child complaining of a sore throat. 62% of PP never performed routine physical examinations of their children. Likewise, 54% of PP did not complete school/sports participation forms. Prescription medications were prescribed for children by 65% of PP. However, only half of the respondents considered the physical exam in their decision to use antibiotics. For children treated with antibiotics, 42% of parents rarely or never notified the child's MD so the event could be recorded in the child's health record. Also, 29% of PP self-referred their children to a specialist without consulting the child's MD. Analyses of treatment by the PP were performed comparing level of physician training, physician sex and primary care (pediatrics, internal medicine, family practice, emergency room) vs all other specialties. Primary care physicians consulted the child's MD for advice less often when their child was febrile ($p = 0.001$) and other physicians completed school/sports forms more frequently ($p = 0.04$). Physicians gave a variety of reasons for treating their own children with convenience listed as most important for 72% of PP and confidence in their own diagnostic and treatment skills as most important for 21% of respondents.

Poster No. 178

Vulnerable Infants and Doctor-Shopping: Common Psychosocial Determinants?

A. Okun and R. E. K. Stein

Department of Pediatrics,
Albert Einstein College of Medicine, Bronx, NY,
and Division of Ambulatory Pediatrics,
Bronx Municipal Hospital Center

Mothers who view their children as "vulnerable" may use medical services erratically, seek care from different doctors, or make emergency room (ER) or other unscheduled visits with seemingly minor complaints. Similar use patterns are associated with maternal psychological distress and, in adult services, with the need for social support. We hypothesized that postpartum women who reported greater levels of psychological distress and inadequate social support would view their infants as more vulnerable and display inconsistent patterns of pediatric medical care use.

Postpartum mothers of infants in the well-baby nursery of an urban, municipal hospital were interviewed and given Ilfeld's Psychiatric Symptom Index and five original questions about the quality of anticipated social support. Telephone interviews were conducted 3-4 months later to obtain details of the infants' medical encounters and administer Kemperer and Forsythe's Vulnerable Child Scale.

169 subjects were enrolled, and 121 (72%) were reached for follow-up. Mothers who perceived their 3-4 month-old infants as more vulnerable had greater levels of postpartum psychological distress ($r = .26$, $p < .01$) and had anticipated being subjected to more frequent demeaning remarks or worrisome advice ($r = .33$, $p < .001$). 30 (25%) mothers visited more than one doctor for a regular check-up, 59 (49%) made unscheduled walk-in visits, and 37 (30%) made ER visits, 6 with minor complaints. A trend toward higher levels of postpartum psychological distress existed among those who made ER visits with minor complaints. Psychological and social variables bore no other associations with specific medical care use patterns.

These findings support the hypothesis that certain social and psychological factors contribute to the development of a mother's perception of her infant as vulnerable. Further research is needed to determine if these in turn lead to different patterns of medical care use later in childhood.

Poster No. 179

Agreement of the Mother's and Physician's Perception of the Child's Health Status Correlates With Clinic and Emergency Room Use

M. Irigoyen and M. Goldstein

Department of Pediatrics, Babies Hospital,
and Columbia University, New York, NY

It has been alleged that many emergency room (ER) visits are trivial and primarily due to maternal concern. This study examines how mother's and physician's agreement on the child's health status correlates with ER and clinic use.

We surveyed 600 mother-physician pairs at the time of a scheduled visit at a pediatric clinic. The patient population was minority (70% Hispanic, 30% Black) and poor (82% welfare). Mothers and physicians were each asked to separately rate the child' health status: 1) how is the overall health of the child?, 2) does the child have a specific health problems?, 3) does the child get sick easily?, and 4) how worried are you about the child's health? On the basis of these ratings, children were categorized into one of three groups for each measure of health: mother and physician agree the child's health is poor, mother and physician disagree, and mother and physician agree the child's health is good. For each of the four measures of health status, when the mother and the physicians agreed that the child's health was poor, there was higher ER and clinic visits. Conversely, when they agreed that the health was good, there was lower ER and clinic visits. When the mother and the physicians disagreed, the number visits to ER and clinic was intermediate. (Sick easily for clinic and ER visits $p<0.05$, worry for clinic $p<0.001$, health problems for clinic $p<0.05$).

In conclusion, in this inner city population, the agreement and disagreement in the perceptions of children's health status by mothers and pediatricians correlated with visits to pediatric health services. This study provides evidence that the increased number of visits made by some children is warranted by their poor health and is associated with physician as well as maternal concerns for their health.

Poster No. 180

Parenting Stress in Families of Urban Third Graders

L. S. Grossman, M. M. Kappelman, and R. G. Chernoff

Department of Pediatrics,
University of Maryland School of Medicine, Baltimore

Pediatricians have been well trained in counseling parents of infants and toddlers regarding parenting. Substantially less attention is paid to counseling parents of school age children. This study was designed to identify the stressful areas in parenting for inner city families of elementary age children.

Parents of 146 randomly selected 3rd grade children were invited to complete the Parenting Stress Index (PSI). The female caretakers (96) or fathers (2) came in for 98 children (67% participation). Participants and non-participants were identical in race, sex, and achievement test results. The schools supplied demographic and school function information.

Study families did not differ significantly from the more middle class normative sample on PSI Total Stress, Parent Domain, or Life Stress scores using 95% confidence intervals. Study families did have significantly higher scores on the Child Domain portion of the PSI ($p<.02$). On subscales, parents of this urban sample felt their children were less acceptable ($p<.01$), more demanding ($p<.05$), moodier ($p<.01$), and less likely to reinforce them in their role as parents ($p<.001$) than norms. Parent subscales were similar to norms except these parents felt less depressed ($p<.02$), less attached to their children ($p<.05$), and less restricted in their lives ($p<.01$). There were no significant differences in responses

ased on child's sex or race. Parents whose children were per-
orming poorly in school (achievement tests below grade level or
nrollment in special education) were more likely to report
arenting stress (parent domain, p<.04; child domain, p<.001)
han those doing well.

This study suggests that there are areas in which parents of
chool age children could benefit from counseling. These include
eaching about "normal" behavior, helping parents see the pos-
tive features of their child, and assisting parents to help their
hild be successful in school.

oster No. 181
laternal Emotional Response to ow Birthweight vs Healthy Infants: ole Of Social Support

. J. Hershman, H. T. Ireys, and E. J. Silver

ediatrics/Albert Einstein College of Medicine,
reventive Intervention Research Center, Bronx, NY

Despite previous work, the relationship between social sup-
ort and the mental health of mothers of low birthweight (LBW)
fants remains poorly understood. This study investigated how
others' psychological responses to the birth of full-term or pre-
ature infants were influenced by the need for the availability
f social support. 22 mothers of LBW infants and a comparison
roup of 27 mothers of full-term healthy (FTH) infants were in-
rviewed in person within 48 hours after birth and by telephone
bout 4 weeks later. The sample consisted of black, Hispanic, and
hite mothers from mid to low SES. Mental health was measured
y the Psychiatric Symptom Index (PSI); social support variables
ere derived from 13 structured items related to need for and
vailability of support.

At T1, mothers in both groups had moderate to high psychiatric
mptoms. Both groups decreased symptoms at T2 but mothers
f the FTH infants decreased much more in total PSI scores
$M=18.7$ at T1, 7.0 at T2) in comparison to mothers of LBW in-
nts ($M=20.6$ at T1, 11.7 at T2). Mothers of the FTH infants
ored lower at T2 than mothers of LBW infants on the PSI anxiety
bscale (4.2 vs 10.2, $p<.05$) and on the depression subscale (8.8
15.5, $p<.10$). The mean number of support items needed by
others in both groups was similar at T1 ($FTH=6.2$, $LBW=5.9$)
d did not change at T2. In both groups, the need for social
pport was modestly correlated with PSI total scores at T1
$=.22$, FTH; .31, LBW) and more strongly associated at T2
$=.52$, FTH; .61, LBW; $p<.01$). The mean number of items re-
ted to availability of support was also similar in both groups at
1 ($FTH=12.4$, $LBW=12.3$) and did not change at T2. Availability
support was inversely related to PSI total scores in the mothers
LBW infants at both T1 ($r=-.47$, $p<.05$) and T2 ($r=-.50$,
$<.05$), but was unrelated at either time in mothers of FTH in-
nts.

It appears that (1) the need for support is similar in both groups
er time, with greater need associated with poorer mental health
d (2) for mothers of LBW infants only, less available support
associated with more psychiatric symptoms.

oster No. 182
hird Trimester Maternal Psychosocial Factors d Home Stimulation for 4 Month Old Infants: Prospective Study

M. Pascoe and J. French

epartment of Pediatrics,
niversity of Wisconsin, Madison, and
epartment of Human Ecology,
ichigan State University, East Lansing

PURPOSE: To examine the association between primiparous
others' prenatal psychosocial factors and the amount of home
imulation provided to their 4 month old infants.

METHOD: A group of primiparous mothers ($N=60$) from
mmunity-based public and private prenatal clinics were studied during the third trimester and about 4 months after delivery to identify antecedents of higher levels of home stimulation during the first few post-partum months. All mothers in this study vaginally delivered normal newborns. The following variables were assessed at a third trimester prenatal visit: maternal demographic characteristics, social support (Maternal Social Support Index), maternal depressive symptoms (Center for Epidemiologic Depression Scale), as well as satisfaction with the male support figure (Dyadic Adjustment Scale). Home stimulation was measured 4 months after delivery during a home visit using Caldwell's Home Observation for Measurement of the Environment. Data analysis included descriptive statistics, zero-order correlations, and hierarchical regression.

RESULTS: Age range was 14-35 years ($median=20$ years), 78% had at least a high school education, 48.9% were single, never married, 76.1% were white. Third trimester social support ($r=.27$, $p=0.009$) and satisfaction with the male support figure ($r=.45$, $p=0.0001$) both had significant, positive correlations with home stimulation at 4 months. Maternal depressive symptoms were inversely, but not significantly, correlated with home stimulation ($r=-.12$, $p=0.26$). Using hierarchical regression, social support and satisfaction with the male support figure continued to explain a significant amount of variance in home stimulation after maternal age, education and socioeconomic status (Hollingshead) were included in the model (Total $R^2=.47$, $p=0.0001$).

CONCLUSION: Mothers' prenatal social environments are associated with their abilities to provide their infants with stimulating home environments. Subsequent research should investigate cost-effective interventions designed to support mothers as they strive to provide stimulating environments for their infants.

Poster No. 183
The Prevalence of Behavioral and Psychosocial Problems in Pediatric Practices

P. J. Leaf, S. M. Horwitz, J. M. Leventhal, and K. N. Speechley

Department of Epidemiology & Public Health,
Yale University School of Medicine,
New Haven, Conn

The prevalence and age specific patterns of psychosocial (PS) problems in pediatric practices has been the subject of considerable debate. We investigated rates and patterns of PS problems as part of a study of the detection of these problems by pediatric clinicians. We administered the Child Behavior Checklist to adults accompanying 1886 consecutive children ages 4-8 seen in the 19 different pediatric practices in South-Central Connecticut. Settings included pre-paid group practices, health centers, and solo and group practices.

Overall 17% of all the children seen, 13% of children ages 4-5 and 21% of children 6-8 years of age scored above the standard cut-point for the CBCL. Girls and boys had similar rates of problems in both the younger (13% vs. 14%) and older (22% vs 21%) age groups. Age related differences were least for the internalizing problems, 5% for children 4-5 years old vs. 6% for children 6-8 years old. Externalizing problems were more common in the older than younger children (6% vs. 3%).

There was some variation by age and sex in the specific CBCL sub-scales with the schizoid scale showing the highest rate of problems for boys ages 6-8 (10%) and the aggressive scale producing the highest rates of problems for boys 4-5. Over 10% of the girls ages 6-8 scored above the standard cut-point for the depressed sub-scale and hyperactivity was the most common problem for girls 4-5. These findings confirm that a significant number of children seen by pediatricians have disorders similar in nature and severity to those treated in child guidance clinics. Further, they show that even within a narrow age range, there are major differences in the patterns of PS symptoms.

Poster No. 184

The Relationship Between Maternal Self-Reporting Health Status and Maternal Report of Children's Health Status Among Hispanics

F. Mendoza, G. Takata, K. Baisden,
L. Herrera, and R. Martorell

Department of Pediatrics and the Food Research Institute,
Stanford (Calif) University

The percent of Mexican-American and mainland Puerto Rican mothers who perceive their children to be in poor health, 18.0% and 19.3% respectively, is significantly higher than the rates reported by non-Hispanic mothers. This study examined the hypothesis that these higher rates were associated with mothers' perception of their own health status. Data from the Hispanic Health and Nutrition Examination Survey were used to identify 1,183 Mexican-American and 332 mainland Puerto Rican mother-child pairs. Mothers reported on the perceived health status of their children (6 months to 12 years) and of themselves. Poor health status was reported by 32.4% of Mexican-American mothers and 38.9% of Puerto Rican mothers. These prevalences were affected by the mother's socioeconomic status ($p<.01$), educational level ($p<.001$), and the presence of a chronic illness ($p<.001$). In addition, for Puerto Rican mothers, marital status was also a significant determinant of perceived poor health status ($p<.01$), while acculturation was a determinant for Mexican-American mothers ($p<.001$). Bivariate analysis showed that mothers' perception of their own health status significantly influenced their perception of their children's health status ($p<.001$) for both groups. However, logistic regression indicated that this was true only for Mexican-Americans after other sociodemographic variables were considered. These findings will be important in assessing the reported health care needs of Hispanic children.

Poster No. 185

Life Change Events, Disease Course, ESR, and CRP in Patients With Juvenile Arthritis

D. M. Siegel, J. Baum, and S. P. Ellis

Department of Pediatrics,
University of Rochester (NY)
School of Medicine and Dentistry

The relationship between stressful life events and the course of many childhood chronic illnesses remains unclear. We conducted a study to test the hypothesis that life change events are associated with the course of juvenile arthritis (JA). Forty-two children, ages 2-20 years (mean age 10.1 years) attending the rheumatology clinic for a scheduled appointment were consecutively enrolled and followed for 6 months at 3 month intervals (total of 3 visits). Data gathered at each visit included: Coddington Life Events Scale, count of involved joints at time of visit, parent and patient assessments of status over the preceeding 3 months (much worse, worse, same, better, much better), ESR and CRP. Data Analysis utilized Chi Square and Pearson Correlation.

All subjects experienced at least 1 change in disease status (increase or decrease in the number of involved joints) over the 6 month period. Whereas life events scores (LES) did not correlate with the number of involved joints at the previous, same, or next visit, parent's global assessment of the child's arthritis status was correlated with LES at the same visit (Chi square $= 5.98$, $df=2$, $p=.05$). LES did not correlate with ESR or CRP at the same visit, LES from visits I and II were correlated with ESR (but not CRP) at visits II and III, respectively ($R^2=.401$, $p=.006$).

These data suggest that stressful life events are not associated with the course of JA as measured by clinically apparent changes in the number of inflamed joints, but they may influence the degree of inflammation as assessed by some laboratory measures. In addition, stress as measured by Coddington's scale, appears to be associated with parents' perception of their child's disease course.

Poster No. 186

The Preceptor Report Form: An Assessment Tool for Use in Evaluating Residents in Ambulatory Pediatric Settings

J. K. Davis and B. Hermosa

Department of Pediatrics, New York Medical College,
Lincoln Medical and Mental Health Center, Bronx

Rating scales are widely used to assess on-the-job performance in medical education. We developed a 15-item scale for use by preceptors to assess clinical competence, interpersonal behavior, and personal responsibility of housestaff in the ambulatory pediatrics setting. This study was to determine if each of these dimensions could be reliably assessed. Thirty-six residents received ratings for the first quarter of 1990-1991 from each of two team preceptors. A principal axis factor analysis with varimax rotation yielded only two factors: interpersonal behavior (makes certain parent and patient know his/her name, communicates pleasure in seeing them, demonstrates sensitivity to feelings, etc.) and clinical competence (shows good clinical judgement, is able to formulate a sound diagnostic hypothesis, is accurate and thorough in maintaining charts, etc.). Internal consistency reliabilities were quite high ($\alpha = 0.90$ and $\alpha = 0.97$). Interrater agreement was significant ($r = 0.35$, $P < .05$ and $r = 0.44$, $p < .01$). Contrary to expectation clinical competence scores did not show significant correlation with American Board of Pediatrics Intraining Exam (ITE) scores. It is concluded that preceptors can reliably assess two dimensions of resident performance early in the academic year. Interrater agreement is expected to improve as the year progresses. With this increased precision of ratings, correlation between clinical competence and ITE scores should also improve. A mid-year replication is in progress.

Poster No. 187

The Care Giving Role: Influences of Residents' Background Characteristics

M. E. Zondorak-Perez and R. E. K. Stein

Department of Pediatrics,
Albert Einstein College of Medicine,
Division of Ambulatory Pediatrics,
Bronx (NY) Municipal Hospital Center

Little is known how background characteristics affect attitudes towards the care giving role among pediatric trainees. As part of a larger study about resident characteristics and continuity in a primary care setting, we developed a 21-item scale to measure positive care giving attitudes and related self-reported behaviors. It has high internal reliability (Cronbach's $\alpha = 0.82$) as does a 7-item psychosocial subscale ($\alpha = 0.80$). 53 of 56 residents (including 45 pediatric and 8 triple board residents: pediatrics, psychiatry, and child psychiatry) caring for patients in a large municipal university affiliated pediatric primary care clinic completed a self-administered demographic questionnaire and the scale.

There were no significant differences on total scale score or psychosocial subscale by race, marital status, number of children, educational loans, sibling number, training level, or foreign vs US medical school training. However, total scale scores were significantly higher ($p<.05$) for women, and residents with work experiences with children, additional graduate degrees or programs, or plans to work in a socio-economically depressed area. Scale scores did not differ by self-perceived adequacy of preresidency preparation for interviewing, emotional support from colleagues, or perceived ability to get needed information by interviewing. Total scale scores did differ significantly ($p<.05$) by previous job experience involving interviewing, medical school interview training, and perceived emotional support from noncolleagues. Pediatric residents scored significantly lower on the total scale ($p=.003$) than triple-board residents.

The higher scale scores among residents who have reported additional interviewing experiences, graduate training, or employment experiences with children raise important educational ssues in the training of pediatric residents. Further study is ıeeded to investigate the possibilities of affecting care giving atitudes with strategic supplemental training opportunities.

'oster No. 188
ledicaid During the Reagan Years: ederal and State Reforms

. D. C. Cartland

)epartment of Research,
\merican Academy of Pediatrics, Elk Grove Village, Ill

As states gain more and more control over health and welfare)olicy, it becomes increasingly important for child health advoates to gauge whether state governments are more or less likely han the federal government to take a conservative approach to ietting policy that affects children's health.

Many researchers have examined whether states have the ca)acity or the will to establish generous welfare policy indepenlently of the federal government. This study analyzes the effect)f federal and state Medicaid policy changes, state economic and state social conditions on state Medicaid and AFDC eligibility)olicy output during the Reagan years.

States' AFDC need standards are examined for the years 1978 hrough 1983, during which time the need standard was reduced)y the states from an average of 60% of states' per capita income o 45%. Medicaid eligibility thresholds for first-time pregnant vomen are examined for the years 1983 through 1988, when the ligibility threshold increased from 54% of states' per capita income to 72%.

Pooled regression is used to analyze states cross-sectionally as well as longitudinally. When controlling for the unemployment rate, age distribution, region, and various Medicaid program haracteristics, the multivariate analyses indicate that, while states may not require federal mandates to increase the generosity of their Medicaid programs, they do require a federal commitment to share the costs of these programs in order to expand them. The findings show that without evidence of a federal commitment, states are likely to compete with each other for lower welfare loads by reducing the generosity of their Medicaid programs.

These findings indicate that child health advocates will be most effective if they attempt to influence both state and federal governments for more generous child health policy in the coming years.

Poster No. 189
Linking Medicaid and Special Education in a Rural State

C. Field, R. Kirby, and T. Nosal

Department of Pediatrics,
University of Arkansas
for Medical Sciences, Little Rock

P.L. 100-360 (1988) for the first time allowed Medicaid (MA) reimbursement of medically related special education (SE) services, but has resulted in limited participation by schools. We describe the successful implementation of an assistance program by a university Department of Pediatrics to public schools using MA. In Arkansas for 1989-90, the mean percent eligible for MA across school districts was 6.6%. The average SE enrollment was 11.0%. The mean percent of SE pupils with speech and language as the primary handicapping condition was 19.4%, the single most common served group.

The professional/technical services for the College of Medicine were made available to schools to assist in obtaining provider status, billing and tracking MA claims for SE services, as well as implementing OBRA 1989 and 1990 changes in MA, especially EPSDT. In the first year, 46 school districts and 8 of 16 3-5 year-old P.L. 99-457 preschool programs in Arkansas began participating as MA providers accessing MA through the Department of Pediatrics. In one district, 19.2% of MA eligibles were in SE programs; MA paid $196/pupil/yr. Participating districts have enrollments ranging from 236 to 6,412 (mean = 1,351), and would have had difficulty billing MA for SE services without assistance and support.

MA funds for SE are not being utilized. Twelve states participated in 1989-90 (four on a pilot basis only), with 22 states projected for 1990-1991 (eight as pilots). Districts this project assisted are rural and small, unfamiliar with MA billing and procedures. P.L. 99-457 funds are payor of last resort; thus MA is vital to the support of early intervention services. This project allows rural schools with limited resources efficient access to MA for SE. Physicians can provide MA expertise to schools as the relationship between the MA and SE entitlement programs evolves. This improves services to children at risk from both low income and educational handicaps.

JOINT TOPIC SESSIONS
Tuesday, April 30, 3 PM-6:30 PM
ADOLESCENT MEDICINE

Access to Handguns Among Urban Adolescents

C. M. Callahan and F. P. Rivara

Department of Pediatrics,
University of Washington, Seattle,
and Harborview Injury Prevention and
Research Center, Seattle

Although mortality of urban adolescents due to firearms has risen sharply in recent years, little data are available on adolescents' access to or ownership of handguns, nor are there reliable data on the relationship of access or ownership to demographic characteristics. This study attempted to determine the access or ownership of firearms by urban adolescents. In addition, we hypothesize that access/ownership would be positively related to deviant behavior and inversely related to socioeconomic status.

Data were gathered through a voluntary anonymous questionnaire, administered to third-year students (N = 491) at two Seattle public high schools during non-elective class time (84% responded, 13% were absent and 3% refused to participate).

Respondents were judged to have easy access to a handgun if they reported ownership or they believed they could acquire a handgun within a few days. A handgun was considered inaccessible for those reporting that acquisition would be difficult or their need for a handgun was unlikely.

Half of the sample was male. Of the males, 6.8% reported carrying a handgun to school. Thirty-five percent reported easy access, and of these, 10% reported having fired the handgun at another person. Easy access to handguns was positively related to gang membership (OR 9.1, C.I. 3.1, 31.3), expulsion from school (OR 4.2, C.I. 2.2, 7.8), crimes against persons (OR 5.0, C.I. 2.7, 9.6) and crimes against property (OR 7.7, C.I. 4.6, 12.6).

The availability and use of handguns by high school juniors is common and for some students handguns are integrated with other risk-taking behaviors.

Risk Factors for Repeat Adolescent Childbirth

L. E. Heery, M. J. Werner, and R. M. Brayden

Department of Pediatrics,
Division of Community Pediatrics,
Vanderbilt University, Nashville, Tenn

Repeat childbirth to an adolescent mother may exacerbate the adverse social, educational, and economic consequences of adolescent parenthood. To identify risk factors for rapid repeat delivery, we evaluated data collected during initial pregnancy on 186 low socioeconomic nulliparous adolescents enrolled in an observational cohort study. Subjects were randomized either to routine care or to an invervention clinic offering comprehensive medical care and psychosocial support from entry into prenatal care until the child's second birthday. Subjects were 13-18 years old (mean = 16.3 years, SD = 1.3), 44% black, 56% white, and 24% married. State vital statistics records searched for 3 years following the initial delivery revealed repeat delivery rates of 19.4% at 2 years, and 31.5% at 3 years after first delivery. Repeat delivery at 2 or 3 years was not associated with marital status; however, black race and younger maternal age were associated at 3 years ($p<.04$ and $<.03$ respectively). Fewer years of education was associated with repeat delivery at both 2 ($p<.01$) and 3 ($p<.001$) years. Later entry into prenatal care for the initial pregnancy was associated with repeat at 2 years ($p<.04$), and approached significance at 3 years ($p=.06$). Seventy-eight subjects were administered the Tennessee Self Concept Scale. As a group, their mean self-concept score did not differ from the normative population; however, repeaters had significantly lower self-concepts than non-repeaters at 2 ($p<.02$) and 3 years ($p<.03$). Enrollment in the intervention clinic had no significant effect on the rate of repeat delivery. Addressing educational and self-concept issues with pregnant adolescents may help reduce repeat deliveries; whereas, comprehensive prenatal and child care alone does not appear to be effective.

Predictors of Depression and Substance Abuse in Adolescent Offspring of Former Teenage Mothers

S. M. Horwitz, L. V. Klerman, and J. F. Jekel

Department of Epidemiology and Public Health,
Yale University School of Medicine,
New Haven, Conn

Children born to teenage mothers are reported to have more behavioral and emotional problems than children born to older mothers. Most of the evidence concerns preadolescent children, and virtually nothing is known about the psychiatric morbidity of these children as they pass through adolescence. We examined the rates and predictors of two important mental health outcomes, major depression and substance abuse in adolescents born to 154 (13-18 yr.) black primiparas enrolled in an early (1967-69) program for school-age mothers. We located 128/149 living mothers (86%) and interviewed 121 (95%). Of the adolescents born to these women, 2 could not be interviewed, 2 refused, 6 were not located, and 111 were interviewed (92%).

Of these 111 adolescents, the mean age was 18, 42% were females, 83% had completed or were in high school, 62% lived with their mothers, and 74% were employed. Four females (8.5%) and 1 male (1.6%) met DSMIII criteria for major depression (MD). Seven males (16.3%) met criteria for substance abuse (SA). Predictors of SA and MD were similar for mothers' 20-year success (RR=4.5, 11.0 respectively) and low fertility (RR=3.7, 11.0). The predictors differed for gender (female sex, RR=4 for MD; male sex, RR=11.5 for SA), contact with grandmothers (RR=3.7 for SA only), and divorce (RR=12.2 for SA only). Because SA and MD had two common predictors and the outcomes were rare, we constructed risk categories with the two outcomes merged.

Using these variables (with the exception of gender), we constructed (4) risk categories with increasing probability of developing SA or MD: 1=3% (2/73), 2=13% (3/24), 3=38% (3/8); 4=80% (4/5). Low risk offspring had mothers who were unsuccessful in the 1967-69 program regardless of other variables. The highest risk adolescents had low contact with their grandmothers, and had mothers who were: 1) successful in the 1967-69 program; 2) divorced; and 3) had few children.

We concluded that these adolescents have considerable psychiatric morbidity and that losses of important emotional relationships are strongly related to this morbidity.

Evaluation of Sexual Behavior in Sports Preparticipation Examination

B. J. Foch, M. K. Oh, C. H. Hong, B. C. Cotton,
B. C. Brown, and R. A. Feinstein

Department of Pediatrics,
University of Alabama at Birmingham

Adolescent males infrequently utilize the health care system. One reason they do seek medical care is for the sports preparticipation evaluation (PPE). The purpose of this study was to determine the feasibility of taking sexual history during PPE, and usefulness of such information in health care delivery. The subjects consisted of 657 males (mean age 16.6 yrs; 12-20 in range) seen during one week of station-oriented PPE at the Adolescent clinic of UAB. 370 (56.3%) were black, 233 (35.5%) white, and 54 (8.2%) of unknown race. 148 (22.5%) were under 15 years of age. Each subject was asked about his sexual experience (history of intercourse; age at first sex; number of lifetime sex partners; condom use in past 4 months, always, sometimes, never; and history of STD) in the Abdomen-Genital station.

Sixty-two percent (407/657) were sexually experienced. Mean age of this group was 16.0±1.1 yrs (compared with 14.8 yrs, of those who never had sex), age at first sex 13.3±1.9 yrs and number of lifetime sex partners 5.5±6.2. 84% of blacks and 34% of whites were sexually experienced. Blacks tended to start intercourse at a younger age (13.0±1.9 vs 14.4±1.7, p=.0001) and have more sex partners (6.1±6.3 vs. 3.6±6.0, p=.001). Only 15% reported a consistent condom use. Condom use was significantly less prevalent among blacks (p=.002). 50% of sexually active blacks and 38% of whites had "never" used condoms, 11% of blacks and 21% of whites used "always" and the rest "sometimes". A history of an STD was reported by 4% of whites and blacks.

Prevalent high risk sexual behaviors (early age of sexual intercourse, multiple sex partners, and inadequate condom use) we found among Jr. and Sr. high school athletes in this study indicate sexual history and counseling may be an efficient health care delivery measure during PPE to an otherwise inaccessible population. We concluded sexual history taking was a feasible and useful adjunct to the PPE.

BEHAVIORAL PEDIATRICS

The Cry of Colic Facies

R. G. Barr, A. Rotman, J. Yaremko, D. Leduc,
T. E. Francoeur, and B. Katchan

Department of Pediatrics,
McGill University, Montreal, Quebec,
and Montreal Children's Hospital

Pain or pain facies is reported as a criterion in 25% of published descriptions of colic. To determine empirically if the crying facies of infants with colic differs from normals, crying bouts of 38 infants whose mothers considered crying a problem ("colic") and 38 age, sex, parity and ethnicity pair-matched controls were videotaped at home for 10 min. before and after an evening feed. Recording was completed when 2 mins. of crying occurred. On the basis of 7-day pre-validated maternal diaries, "colic" infants were sub-defined as *Wessel's Colic* if cry and fuss duration was ⩾3 hrs/day for ⩾3 days/wk or as *Non-Wessel's Colic* if not. Using the Neonatal Facial Coding System (Gruneau & Craig 1987), tapes were scored without sound and blind to identity, group, and prandial state. Rates of occurrence/120 seconds were determined for 7 facial actions (brow bulge [BB], eye squeeze [ES], nasolabial furrow [NLF], open lips [OL], vertical mouth stretch, horizontal mouth stretch, taut tongue), plus Total Facial Activity (TFA) and "pain concatenation" (simultaneous presence of BB, ES, NLF, OL). Interobserver reliability (kappa) averaged .83 for all measures (range .57 to 1.0). Groups were compared by ANOVA with post hoc Tukey tests.

After feeding, there were no significant differences on any measure. Before feeding, however, Wessel's Colic infants differed from *both* Non-Wessel's Colic and Controls on Total Facial Activity (mean ± SD: 78±7 vs. 63±14 and 68±11 respectively; F[2,56]=5.1, P=.01) and almost on pain concatenation (106±14 vs. 83±30 and 89±24; F=2.9, P=.07). The same pattern occurred specifically for brow bulge (118±3.2 vs. 99±22 and 109±15; F=4.1, P=.02), taut tongue (73±30 vs. 43±34 and 44±33; F=3.3, P=.05) and, probably, nasolabial fold (108±14 vs. 85±29 and 94±25; F=2.8, P=.07).

CONCLUSIONS: Under some conditions, the crying facies of infants meeting Wessel's criteria differs from that of both non-Wessel colic and normal infants. This includes a facial expression often seen with pain stimuli, which may reflect differences in the infants and/or stimulate parental concern.

Reducing Low Birthweight, Depression, and Stress Through Social Support in Pregnancy

A. W. Cross, K. J. Welshimer,
E. Jackson, and J. Chapman

Center for Health Promotion and Disease Prevention,
University of North Carolina at Chapel Hill

Accumulating evidence suggests that stress and social isolation can have a negative impact on pregnancies. The Helping Mothers Program was created in 2 rural counties to reduce low birthweight. Through this program, volunteers were recruited among women already perceived as natural helpers. Training served to enhance the volunteers' helping skills, while providing greater information on the prevention of problems in pregnancy. Volunteers were then paired with pregnant women at risk for low birthweight. The volunteers met regularly with the mothers throughout pregnancy offering friendship, support and assistance.

The frequency and nature of the interactions between mother and volunteer varied greatly among the 116 mother-volunteer pairs. Seventy mothers were interviewed extensively early and late in pregnancy. Mothers experienced a 19% reduction in stress ($p = 0.007$) and 13% reduction in depression ($p = 0.0001$) over the course of participation, which was significantly associated with the number of contacts between mother and volunteer. All 116 program mothers were compared with 3 control groups matched for age, race, parity and education. The first was from the same counties prior to the time of the program. The other 2 were from a demographically similar county prior to and concurrent with the program. In the program counties, the low birthweight rate was 6% among the retrospective control group and remained 6% among program participants. In the comparison county, the low birthweight rate was 7.8% prior to the program and rose to 13.8% at the time of the program which was significantly worse ($p = 0.03$) than the program mothers. For prenatal care, program participants received more prenatal care than mothers in all 3 control groups with that difference being statistically significant when compared with the same county retrospective group ($p = 0.001$).

We conclude that a volunteer social support program in pregnancy can be associated with reduced stress and depression, fewer low birthweight babies and improved prenatal care.

Evaluating A Parent Support Program For Mothers Of Chronically Ill Children

H. T. Ireys, E. J. Silver, R. E. K. Stein,
K. Bencivenga, and C. Koeber

Pediatrics, Albert Einstein College of Medicine,
Preventive Intervention Research Center, Bronx, NY

In view of increased mental health risks for children with serious on-going health conditions and for their parents, many pediatric services have sponsored parent support programs. Few such programs, however, have been evaluated in terms of their impact on parental mental health or child behavior. We postulate that such programs will have a long-term positive effect on maternal mental health by initially enhancing aspects of parental competence and efficacy. We are conducting a randomized controlled trial of a parent support program for mothers of children aged 5-9 years who have serious on-going health conditions. The Parent-to-Parent Network (PTPN) includes three women from the community who have themselves raised children with serious ongoing health problems. PTPN staff provide information, affirmation of the mothers' skills, and emotional support to mothers through bi-weekly phone calls and regular face-to-face contacts for 1 year. Mothers in the study are primarily of minority background and have low to middle income. We have used the Rosenberg Self-Esteem scale (RSE), Sense of Competence subscale of the Abidin Parenting Stress Index (PSI) and the Ilfeld Self-Efficacy scale (ISE) to measure mothers' self-esteem, sense of parenting competence, and self-efficacy, respectively.

In paired t-tests comparing baseline (T1) and 6 month scores (T2), mothers in the intervention group ($N = 64$) had improved self-efficacy ($t = 3.89$; $p < .01$) and improved self esteem ($t = 3.49$; $p < .01$). Mothers in the control group ($N = 31$) did not change significantly on either measure. The control group showed increased parenting stress from T1 to T2 ($t = 2.45$; $p < .05$), but scores of intervention mothers did not change significantly. These results suggest that the PTPN is achieving its initial goals of increasing mothers' feelings of self-worth and control over life experiences and also prevents deterioration in mothers' sense of parenting competence. More work is needed to determine long-term mental health effects of parent support programs for mothers of children with chronic health conditions.

Can the Reliability of Mothers' Clinical Judgments be Predicted?

P. McCarthy, D. Cicchetti, S. Sznajderman,
B. Forsyth, M. Baron, H. Fink, N. Czarkowski,
B. Bauchner, and K. Lustman-Findling

Department of Pediatrics,
Yale University School of Medicine,
New Haven, Conn

The purpose of this study was to identify descriptive data gathered at the two week well child visit which would predict the reliability of mother's clinical judgments during their children's subsequent acute illnesses. It was a pre-existing hypothesis that mothers who a) demographically, were younger, unmarried, on welfare, resided in the inner city, had less education, who b) clinically had fewer previous children, less adult support, previous children with serious illnesses, and who c) psychosocially, had concerns about the pregnancy outcome, higher Spielberger State-Trait Anxiety scores and higher Maternal Anxiety About the Baby Scores would be more unreliable. The study was a randomized trial of the Acute Illness Observation Scales (AIOS); 369 mothers participated, 183 in the Intervention Group, and 186 in the Control Group. There were 704 acute illnesses judged simultaneously and independently by mothers and pediatricians in the 33 months of study. Intervention Group mothers used the AIOS; Control Group mothers a 3 point global assessment scale.

Pearson r correlations were performed between the independent variables, taken singly and in all possible combinations, and the dependent variable, reliability of mothers' judgments as measured by weighted kappa (Kw). Group assignment was entered as an independent variable. Analyses were performed separately for all first, second, and third acute illness visits to control for any "practice effect" (Analysis I). To control for consistency of observers, the first, second, and third visits of mothers with three visits were also analyzed (Analysis II).

Results indicate that, depending on the visit number, adverse demographic, clinical and psychosocial characteristics did correlate with poorer reliability independent of group assignment. The correlations ranged from small (Analysis I, first visit, multiple variable $r^2 = 3\%$) to large (Analysis II, second visit, multiple variable $r^2 = 28\%$). Controlling for both visit number *and* consistency of observers versus visit number alone (Analysis II versus Analysis I) increased multivariate correlations to Kw. Except for one variable, number of previous children, correlations were in the hypothesized direction. The results support the untoward impact that adverse demographic, clinical, and psychosocial factors have on mothers' clinical judgment. These data may assist pediatricians in identifying parents who might benefit from more intensive teaching and support about acute illness episodes in their children.

Cognitive Dysfunction in Children With Post-Meningitic Deafness

D. Kelly, B. Kelly, M. Jones,
S. Verhulst, and S. Bell

Department of Pediatrics, Southern Illinois University
School of Medicine, Springfield,
and Illinois School for the Deaf, Jacksonville

The long term sequelae of bacterial meningitis, including subtle neuropsychologic dysfunction, are not clearly delineated. While hearing loss is the most frequent neurologic complication, it has been suggested that this reflects damage to the inner ear or eighth nerve specifically, without central nervous system involvement. This study utilized a wide range of measurements including computerized neuropsychologic tests to compare the function of children with deafness secondary to bacterial meningitis with hereditarily deaf peers.

Twenty-four prelingually profoundly deaf students (16 males, 8 females) at a residential school for the deaf were studied. Eleven had post-meningitic deafness (mean age 13.2 yrs., mean age of infection 9.8 months). Controls were 13 children with hereditary deafness (mean age 13.8 yrs.). All subjects were of normal intelligence with no other physical handicaps. Measures included medical and neurologic evaluation, IQ and academic achievement testing, behavioral ratings by parents, teachers and dormitory supervisors (Child Behavior Checklist, ACTeRS and ANSER questionnaires), neurodevelopmental testing and computerized testing (visual attention and memory scanning tasks using the MEL system).

Study groups did not differ significantly with regard to medical complications, standard neurologic findings, WISC-R Performance IQ or behavioral measures. However, significant differences were seen on academic and computer tests with the post-meningitic students performing less well on the Stanford Achievement Tests (Math: $t=2.76$, $p=.014$); reaction-time on the visual attention test ($t=2.13$, $p=.045$); and accuracy of responses on memory scanning task ($t=2.87$, $p=.009$). The accuracy measure correlated significantly with achievement scores.

Thus, while general psychologic and neurologic assessment did not reveal differences, more precise measures of cognitive processing efficiency did show dysfunction in students with post-meningitic deafness which was also reflected in their academic achievement. These findings suggest that nervous system damage in children with post-meningitic deafness is not isolated to the eighth nerve.

EPIDEMIOLOGY AND PREVENTIVE PEDIATRICS

Firearms: Family Attitudes and Household Safety Practices

C. C. Wiley and R. Casey

Division of General Pediatrics,
Children's Hospital of Philadelphia, Pa

This prospective study was conducted to examine firearm safety practices, experience with shootings, and attitudes concerning firearms. We interviewed 208 children (ages 5-12 years) and surveyed 242 parents (92% mothers) from a pediatric clinic and a private group practice. Boys and girls were equally represented. Payment for health care was 51% medical assistance (MA) and 49% private insurance (PI). The MA and PI groups differed by employment (44% vs 84%), college education (30% vs 85%), single parent families (74% vs 16%), race (93% black vs 34% black) and mean maternal age (31.5 vs 37.4 years).

Gun ownership was reported by 10% of parents. The majority of guns were potentially accessible, 36% were not always locked and 18% were sometimes or always kept loaded. Only 3% of parents discussed gun safety with a pediatrician. MA parents were less likely to be in favor of gun control (56% vs 89%, $p<.001$).

Parents underreported their children's toy gun play (44% parents vs 81% children, $p<.001$) and pretend gun play (33% parents vs 53% children, $p<.05$). More boys reported toy gun play but many girls also played with toy guns (93% vs 70%, $p<.001$).

Personal knowledge of shootings was common among children (24%). MA children more often reported shootings of family members or friends (37% MA vs 11% PI, $p<.001$) and were more likely than PI children to have witnessed a shooting (12% MA vs 2% PI, $p<.01$).

Few children felt it was appropriate to shoot animals (27%) or people (6%). Four percent thought they might ever shoot someone. One third of children thought about being shot themselves. Of note, despite the MA children's greater exposure to shooting, all children's attitudes about guns were similar and did not differ by method of payment, income, level of maternal education, site of health care or sex.

We conclude that parents owning guns describe unsafe storage of guns and very few parents report having had anticipatory guidance concerning gun safety. Many children have personal experience with firearm-related violence and think about being shot themselves. Children are similar in their gun play and attitudes about gun use despite disparate socioeconomic backgrounds and exposure to violence.

Previous Injury As A Risk Factor for Youth Suicide

D. C. Grossman, R. W. Soderberg,
and F. P. Rivara

Department of Pediatrics,
Harborview Injury Prevention Center,
University of Washington, Seattle

While suicide attempts are known to be risk factors for later suicide completion, it is unclear whether other injuries are also associated with increased risk of later suicide. It has been widely hypothesized that other intentional or unintentional injuries represent suicide attempts in disguise.

We conducted a population based case-control study to answer the following question: What is the risk of death by suicide for persons ages 10-35 with a past history of hospital admission for a previous suicide attempt, or other intentional and unintentional injuries? We hypothesized that a past hospital admission for both intentional and unintentional injury would be significant risk factors for eventual suicide.

Cases were all Washington State residents ages 10-35 whose death certificate indicated suicide as the cause of death during 1987-89. Controls were a sample of licensed drivers in Washington State matched by age, sex, race and zip code. Exposure to previous injury was ascertained by linking cases and controls to a statewide hospital database (CHARS) of all civilian hospital admissions over the same time period. Using the ICD-9 E-codes, hospitalizations were classified as related to suicide attempts (SA), unintentional injury (UI), and other intentional injury of intentional or undetermined intent (II).

Of the 838 cases, 81% were male. Eighteen percent of the cases and 4% of the controls had a record of a hospital admission in the CHARS database during the exposure period. Among cases, there were 9 persons with a past admission for *UI*, 29 with a past *SA*, and 9 with a past *II*. In contrast, the controls only had 14 *UI* (3.0%), 3 *SA* (3.0%) and 5 admissions for *II*. Compared to controls, cases were more likely to be exposed to hospitalizations for suicide attempts (OR=48, 95% CI=14-198), unintentional injury (OR=3.1, 95% CI=1.3-6.9), and injuries of intentional or undetermined intention (OR=9.0, 95% CI=3-31).

We conclude that, compared to controls, adolescent and young adult suicide victims have a small but significant history of both intentional and unintentional injuries resulting in a hospitalization prior to their death. These findings support the hypothesis that the increased rate of injury in this population may represent additional suicide attempts.

Effects of Screening Children for High Cholesterol

C. M. Lannon and J. A. Earp

Department of Pediatrics, School of Medicine,
and Department of Health,
Education, and Health Behavior,
School of Public Health,
University of North Carolina, Chapel Hill

Many pediatricians are enthusiastically instituting cholesterol screening despite controversy about the long-term implications of an elevated cholesterol level in children. The American Academy of Pediatrics (AAP), concerned that screening may lead to mislabeling and overly restrictive diets, stresses laboratory confirmation and nutritional follow-up for children with elevated cholesterols. We studied parents' behavior and attitudes toward screening children for high cholesterol.

During an eight-week period in summer of 1989 all children between the ages of 2 to 15 years seen for well-child examinations at a community pediatric group practice were offered cholesterol screening by fingerstick method. Most parents were well-educated and white.

Of 440 children screened, 134 (30%) had cholesterol levels above the recommended cutpoint of 175 mg/dl (75th percentile). Parents were notified of results and encouraged to comply with AAP guidelines. Only sixty-four children returned for follow-up; hypercholesterolemia was confirmed in 97% of children with screening values > 199 mg/dl (95th percentile) and in 76% with values between 175 and 199 mg/dl. Parents of the children with high screening levels who did not return for lipid panels (N = 70) were interviewed by telephone; 86% responded. Reasons for non-compliance included "not sure test machine was accurate" (67%); "child too traumatized by fingerstick" (47%); and "will try low-cholesterol diet before recheck" (40%). A third of these parents (N = 20) felt that confirmation of an elevated cholesterol "would make the child worry too much." Only 29 of 101 parents of children with high screening levels (29%) talked with a dietician. In a follow-up of this cohort, we will evaluate whether identifying children as hypercholesterolemic has affected parents' health perceptions of their children (labeling) and family habits.

In this middle-class, well-educated population, a large proportion of children had elevated screening cholesterols, but few complied with AAP guidelines. As a result, many children may be mislabeled as hypercholesterolemic and may not benefit from screening.

Access to Care for Poor and Nonpoor Children: Separate and Unequal?

R. F. St. Peter and P. W. Newacheck

Robert Wood Johnson Clinical Scholars Program,
Department of Pediatrics
and Institute for Health Policy Studies,
University of California, San Francisco

Access to care for poor children has improved since the implementation of Medicaid. Recent legislation expanding Medicaid eligibility will significantly increase the number of children covered by this program. We examined how coverage by Medicaid affects the use, location, and continuity of care for poor children. The findings reported are from data in the 1988 National Health Interview Survey, which contains information on 17,110 children under 18 years of age.

Poor children with Medicaid were more likely than uninsured poor children to have a regular source of care (93% v 76%, $p<0.001$) and to receive routine care within an appropriate time interval (85% v 66%, $p<0.001$). However, poor children with Medicaid were less likely than nonpoor children to identify a doctor's office as their regular source of care (57% v 82%, $p<0.001$), and more likely to identify a hospital clinic (12% v 3%, $p<0.001$) or neighborhood health center (15% v 3%, $p<0.001$). Those children receiving routine care at a neighborhood health center rather than a doctor's office were 12 times more likely to receive sick care at a different location than where they receive routine care (37% v 3%, $p<0.001$). Such children were also 5 times more likely to identify an emergency room as their regular source of sick care.

While Medicaid does improve access to care for poor children, it does not ensure that they have access to the same locations and continuity of care as nonpoor children. Future legislation designed to improve access to care for poor children should also address the separateness and inequality of care to which these children gain access.

GENERAL PEDIATRICS AND PEDIATRIC EDUCATION

Has the Eighty Hour Work Week Lessened Stress Levels in PL-1 Residents?

J. E. Berkelhamer and N. H. Pliskin

Departments of Pediatrics and Psychiatry,
Wyler Children's Hospital,
University of Chicago (Ill)
Pritzker School of Medicine

We investigated whether implementation of the Association of American Medical Colleges recommendations on work hours lessened stress levels in first year pediatric residents. The Holmes and Rahe Social Readjustment Rating Scale (HRSRRS) and the Farguhar Stress Questionnaire (FSQ) were administered to two groups of PL-1 residents (1988 and 1990) and results were compared. After July 1, 1990 rotations have averaged no more than 80 hours of work per week; residents are relieved of duties one 24 hour period per week and when displaying signs of fatigue.

23 of 24 1988 participants and 17 of 19 1990 participants returned completed HRSRRS forms. The mean scores were 296 (sd = 121) and 272 (sd = 129) respectively, both well into the "moderate" crisis range defined by the test instrument (200 to 299). The mean scores showed no significant difference using the t test for independent samples. The number of positive responses to those most frequently cited items did not differ significantly between the 1988 and 1990 groups (Chi square = ns). Using weighted HRSRRS point values (pv), the most contributory factors to overall stress levels in both groups were change in responsibilities at work (pv = 24), change in financial state (pv = 22), change in work hours or conditions (pv = 18), end of school (pv = 18), change in living conditions (pv = 16), change in residence (pv = 13), and change in sleeping habits (pv = 12).

All 1988 (n = 24) and all 1990 (n = 19) residents returned completed FSQ scores. The mean scores were 7.7 (sd = 3.8) and 7.3 (sd = 3.0) respectively, both within the "average" stress range of 6 to 9 points defined in the test instrument. The mean scores showed no significant difference using the t tests for independent samples. The FSQ scores demonstrated that both resident groups were in the average range in terms of symptomatology due to stress, suggesting that both groups were coping well considering the stressful demands of residency training.

The results of this study do not support the contention that the eighty hour work week alone will lessen resident stress.

Diagnostic Trends in a Pediatric Primary Care Clinic

C. Calderon, G. Gonzalez, and M. Valcarcel

Pediatric Department, University of Puerto Rico,
Recinto Ciencias Medicas, San Juan

A major goal of General Training Programs is to teach trainees to diagnose and manage the common pediatric morbidity. Many programs have increased the ambulatory experience, providing exposure to the changing morbidity pattern, including the management of psychosocial and psychosomatic conditions. Since 1979 a model General Pediatric clinic has been operational in Cataño, Puerto Rico, serving as a clinical training site with emphasis on ambulatory, preventive, and biopsychosocial aspects of pediatric care. A retrospective and descriptive study was done with the purpose to identify the diagnoses to which the trainees have been exposed in this population and changes in the patterns of these diagnoses. Data collected included: number of patient-doctor contacts, type of patient visit, patient age, frequency of diagnoses, and patient absenteeism. A patient-doctor contact was defined as that occurring during a first visit to clinic, follow up, or urgent care visit. Diagnostic patterns were compared between each year. A total of 66,054 patient-doctor contacts occurred in nine years, 79% for scheduled health care visits and 20% for urgent care. The main diagnoses were: healthy child or adolescent (HV), well baby (WB), upper respiratory tract infection (URTI), skin condition (SC), bronchial asthma (BA), acute gastroenteritis (AGE), otitis media (OM), anemia (A), incomplete immunization (II), psychosocial condition (PS), nutritional and/or linear growth problems (N), psychosomatic condition (PC), parasites (P), pneumonia (PN), and others. There was a significant decrease ($p<.005$) in the diagnosis of infectious diseases (URTI, AGE, P, PN), comparing 1979 to 1989. There was a significant increase ($p<.005$) in the proportion of patients with the diagnoses of WB and HV, (two most common diagnoses of 1989). This data supports the curricular goal of exposing the trainees to diagnosis and management of common pediatric morbidity.

Comparison of Interviewing Skills of Fourth Year Medical Students With Their Individual Performance as Second Year Medical Students

R. D. Olsen and B. Anderson

Department of Pediatrics,
Mayo Clinic, Rochester, Minn

There are many articles in the pediatric literature on doctor-patient communications and its effect on parents, but little has been written on the development of interviewing skills in medical students. This study was designed to assess and compare interviewing skills of medical students as they progress from their second to fourth year.

In this longitudinal study a class of 33 students completed videotaped interviews with a simulated parent who had been trained to portray the mother of a child with chronic illness (during their second year and fourth year of medical school). The evaluation process involved: 1) measurement of historical content using a checklist of specific facts; and 2) evaluation of the interview process based on a rating instrument which was subdivided into the following sections: organization, questioning skills, rapport, and closure. Observations were made by pediatric parent-instructors who had been trained to analyze the interaction and had obtained 90% interobserver reliability. During the testing in the fourth year, parent-instructors were blinded to any previous data.

Results: There was generalized improvement in the questioning skills between the second and fourth year ($p = .02$ sign rank). There was no improvement in skills related to rapport-building, which included items such as empathy, support, and nonverbal messages. In fact, there was a downward trend in the rapport-building skills; 9% failed in the second year vs. 18% in the fourth year, and 36% scored skillful in the second year vs. 11% in the fourth year ($.05 < p < .10$, sign rank). There was no significant change in ability to obtain historical information. During the post interview feedback session between the parent-instructor and fourth year medical students, it became evident that as the students progressed through medical school they based their interviewing skills more and more on performance and expectations of the role models—the residents and faculty. They felt their role models were fact-oriented. They did not feel encouraged by the faculty to improve rapport-building skills, nor was this routinely assessed.

Reduction of Morbidity in Asthmatic Children Given a Spacer Device

S. J. Cunningham and E. F. Crain

Department of Pediatrics, Albert Einstein
College of Medicine,
Division of Pediatric Ambulatory Care,
Bronx (NY) Municipal Hospital Center

Spacer devices have made inhaled medication available to young children with asthma. However, their effectiveness is unsubstantiated in settings where ongoing reinforcement is unavailable. We hypothesized that providing a spacer device and a single, brief demonstration regarding its proper use would result in earlier resolution of asthma symptoms, improved school attendance and decreased frequency of unscheduled medical visits for asthma among children receiving noncontinuous care in an urban emergency room (ER).

Children between the ages of 3 through 10 years, who presented to the ER for the treatment of asthma, were randomly assigned to receive either: 1) a spacer device plus inhaled beta agonist or, 2) oral or inhaled beta agonist without a spacer device. Subjects in both groups received other medications at the discretion of the evaluating physician. A questionnaire assessing the child's asthma history was administered to the parent at the time of ER discharge. In follow-up telephone interviews at 1 week, and at 2 and 4 months, parents reported days of wheeze and cough, missed school days and unscheduled medical visits related to asthma.

Ninety-eight patients were enrolled. Eighty-four patients (86%) completed the study. Seven patients from each group were lost to follow-up. The groups did not differ in age, ethnicity, age at onset or baseline severity of asthma. At 1 week there were no significant differences in reported days of cough or wheeze or days missed from school. At the 2 and 4 month follow-up, patients given the spacer device had experienced significantly earlier resolution of cough (4.7 and 2.6 days vs. 11.3 and 6.8 days, $p<.01$) and wheeze (2.3 and 0.4 days vs. 7 and 3.6 days, $p<.001$), and had missed fewer school days because of their asthma (1.2 and 2.5 days vs. 6.7 and 5.7, $p<0.03$). Unscheduled medical visits were reported at similar, low frequencies in both groups.

We conclude that introducing a spacer device to patients in a busy, urban ER is an effective and efficient intervention that improves the functioning of asthmatic children.

An Assessment of Nutritional Status in Homeless Children

J. H. Gould, T. L. Pelham, and J. C. Weiss

Department of Pediatrics,
Jefferson Medical College,
Philadelphia, Pa

The association between poverty and poor health and nutrition is well known. However, to date there has been no comprehensive nutritional assessment of the pediatric homeless population. The purpose of this study is to determine the nutritional status of children living in homeless shelters.

Dietary history, anthropomorphic measurements, and blood studies were obtained from 102 children, ages 0.5 yrs. to 5.6 yrs. (mean = 2.7 yrs.), living in four Philadelphia area homeless shelters. The duration of homelessness averaged 16.5 ± 13.8 wks. Although all of the children were eligible for WIC, only 48 children had been enrolled in the past twelve months. For children greater than one year of age, the primary source of nutrition was meals provided by the shelters.

Anemia (Hgb $<$ 2 SD below mean for age) was found in 23% of children. Iron deficiency (serum ferritin $\leq$ 15ng/ml) was seen in only 5% of anemic children and 4% overall.

Weight for age measurements did not differ significantly from expected NCHC standard norms, and the tricep skinfold measurements were also normal, suggesting adequate caloric intake.

n contrast, 33% of the children had heights below the tenth percentile for age, and 32% had mid-arm muscle area (MAMA) below he tenth percentile, indicating chronic protein malnutrition. Retinol binding protein (RBP), a blood test that measures acute protein malnutrition, was abnormal in 53% of the children. Of he children with MAMA and height above the twenty-fifth percentile, 45% and 53% respectively had abnormally low RBP. Thus, the RBP was able to identify protein malnutrition that would not have been detected by anthropometry alone.

In summary, this study demonstrates that anemia and both acute and chronic protein malnutrition are common in homeless children. These nutritional findings, which did not show statisical correlation with duration of homelessness, WIC enrollment, or percentage of meals provided by the shelter, may be associated with other aspects of homelessness and will require further investigation.

APA TOPIC PLENARY SESSION
Wednesday, May 1, 9 AM-NOON
CLINICAL ISSUES

Double-blind, Cross-over Trial of Psyllium Fiber n Hypercholesterolemic Children

. A. Dennison

Department of Pediatrics, Cornell University
Medical College, and the Rogosin Institute, New York, NY

Water-soluble fiber has been shown to have a cholesterol lowring effect in adults. A randomized, double-blind, placebo-ontrolled, cross-over trial was designed to test the efficacy of psyllium fiber in lowering elevated LDL-cholesterol (LDL-C) levls in children (5-18 years). Subjects with LDL-C levels ⩾ 2.84 mmol/L (110 mg/dL), despite ⩾ 3 months of a low fat, low satrated fat, low cholesterol diet were enrolled. Two ready-to-eat cereals, with psyllium fiber (6 g per day) and without, were precribed for 4-5 weeks each, with an intervening 2 week washout hase. Reported compliance rates exceeded 90% in the 20 subjects completing the study. Mean initial total cholesterol (TC), DL-C, HDL-C, and triglyceride (TG) values were: 5.23, 3.60, .18, and 2.22 mmol/L, respectively. Comparison of the mean hanges (from baseline) in lipid values following the two periods f cereal consumption revealed no statistically or clinically sigificant differences in TC, LDL-C, or HDL-C values. Triglyceride levels, however, increased significantly (0.68 mmol/L 6 mg/dL), $p < 0.05$) after the control cereal, compared to the syllium cereal. No significant differences were noted in the chilren's dietary intake (assessed by 7-day diet records) during the wo study periods. Growth parameters (height, weight, skinfold hicknesses), vitamin (folic acid, Vitamin A, D, and E), and mineral (iron, zinc, and calcium) levels were not affected. In this tudy, psyllium fiber had no additional TC or LDL-C lowering ffect in children who were following low fat, low cholesterol iets.

acteriology of Acute Otitis Media (AOM): A New Perspective

. A. DelBeccaro, P. M. Mendelman, A. F. Inglis,
. A. Richardson, and C. Clausen

Departments of Pediatrics and Otolaryngology,
University of Washington, Seattle

Previous studies have reported 20% to 50% of middle ear cultures from patients with AOM are sterile. We describe our isotion of bacterial pathogens from patients with AOM.

Children were recruited from the Emergency Room, during otolaryngology Clinic hours, as part of a multicenter single blind tudy comparing oral antibiotics in the treatment of AOM. Eligibility required symptoms ⩽ 7 days duration, an erythematous r bulging tympanic membrane (TM), and no antibiotics in the st 5 days. Surface cultures of the TM, and an aspirate of middle ar fluid (MEF) were taken immediately to the microbiology lab nd cultured aerobically. MEF specimens were also cultured anaerobically. If there was no growth on the primary plates a blind subculture of the Tryptic Soy Yeast broth was performed at 48 hours. A positive culture was considered to be a pathogen if it was isolated only from the MEF. If a child had recurrent otitis within 30 days a repeat tympanocentesis was performed.

Forty-one patients between the ages of 6 months and 15 years were enrolled; 27 (66%) were female, 33 (80%) white, and 14 (34%) had health insurance. Thirty-eight (93%) of the 41 patients yielded the following 43 pathogens from their MEF: *S. pneumoniae* 19 (44%); *M. catarrhalis* 11 (26%); *H. influenzae* 9 (21%); others 4 (9%). Ten (91%) of the *M. catarrhalis* and 3 (33%) of the *H. influenzae* strains produced the β-lactamase enzyme. Four patients had > 1 pathogen in their MEF. No growth was observed on the primary plates of 7 (18%) of the 38 positive cultures, but grew from the broth subcultures. Ten (24%) patients had a recurrence, all 10 (100%) were culture positive on repeat tympanocentesis, and 7 (70%) of the 10 had different organisms.

CONCLUSIONS: 1) Bacterial pathogens are recoverable in > 90% of AOM if specimens are promptly cultured and if broth subcultures are used; 2) recurrent infections often are due to new organisms.

Brush Culture Method for Diagnosing Tinea Capitis

T. W. Hubbard and J. M. de Triquet

Department of Pediatrics,
Eastern Virginia Medical School, Norfolk

Tinea capitis (TC) is a common dermatophytosis in childhood. Documenting fungal infection is prudent before starting systemic antifungal agents, but culture methods involving scraping and pulling hairs are time-consuming and cumbersome. A quicker, less painful method for diagnosing TC was tested.

During March to October 1990, 70 children (mean age 5.1 years, range 8 months - 11 years) presenting to the Children's Hospital of The King's Daughters (CHKD) with symptoms suggesting tinea capitis (e.g. alopecia, scaling) were cultured using both the traditional method (TM) and an experimental brush culture method (BCM). First, in the BCM a small, sterile brush (Reach juvenile toothbrush) was gently rubbed over the affected areas; the brush fibers then were gently depressed into the surface of the dermatophyte test medium: ACU-DTM (Acuderm) agar slant, and then discarded. The TM was then used, scraping scale if present and removing hairs from the same lesions, embedding them on another ACU-DTM. The slants were read daily. No color change in 21 days signified a negative result. Positive cultures were subcultured to identify the dermatophyte. There was no significant difference between methods in detecting disease or lack thereof; culture results agreed in 64 patients; in 5 cases BCM was positive, TM negative; in 1 case TM was positive, BCM negative (Wilcoxon, $p > .4$). Of the 51 paired positive cultures, BCM samples turned positive before TM in 39, and later than TM in 12 (9.6 days (BCM) vs. 10.6 days (TM); $p < .01$, T-test). *Trichophyton tonsurans* was the dermatophyte in all cases of TC.

BCM is a reliable, painless, and simpler alternative to TM in culturing a scalp for fungal disease. BCM produces positive results significantly faster and is a more sensitive method than TM in detecting TC.

Utility of Oxygen Saturation in Evaluating the Response to Treatment in Wheezing Infants

A. J. Alario, W. J. Lewander, P. H. Dennehy, R. Seifer, and A. L. Mansell

Department of Pediatrics,
Rhode Island Hospital, Providence

To determine the utility of oxygen saturation measurements in acutely wheezing children, we evaluated 74 full term, previously well infants (mean age 10.1 months) presenting as outpatients with acute wheezing. As participants in a double-blind, randomized, placebo controlled trial infants received nebulized metaproterenol sulfate, as an initial treatment or after a control treatment with normal saline. At baseline and 20 minutes after each treatment a clinical assessment was made which included respiratory rate (RR), and a standardized respiratory distress index (RDI) based on 3 key variables: wheezing, retractions, and flaring. To keep the clinical assessors blinded, oxygen saturations (measured by pulse oximetry) were recorded by a research assistant. Oxygen saturations before and after medication were compared in a post-hoc analysis with the clinical response to treatment defined as *both* a decrease in RR of ≥20% *and* an improvement in RDI score of ≥50% compared to premedication values.

At baseline, the mean (±SEM) oxygen saturation for the entire sample was 94.1±.3% (vs. 97.7±.3% from a sample of healthy controls, P≤.01). Forty-two percent (31/74) of the infants were classified as responding to metaproterenol. No significant difference in oxygen saturation was observed with treatment: pre=94.6±.5% vs. post=95.5±6%, with a mean difference per patient of 0.86%, (CI_{95} = −.34 to 2.06%, P=.15). Forty-six percent of responders showed no change (25%) or a decrease (21%) in oxygen saturation following medication. Likewise, 23% of nonresponders showed no change in oxygen saturation and 27% a decrease. These data suggest that although oxygen saturation measurements may indicate hypoxemia in an acutely wheezing infant, change in saturation may not be a useful determinant of the clinical response to bronchodilators. The deterioration in oxygen saturation with treatment in some infants may be due to vasodilation of under-ventilated areas of the lung, resulting in a decrease in measured oxygen saturation.

Initial Weight Loss and Return to Birth Weight Criteria for Breast-fed Infants: Challenging the 'Rules of Thumb'

S. DeMarzo, J. Seacat, and M. Neifert

Lactation Program, Presbyterian/Saint Luke's
Medical Center, Denver, Colo

Weight loss up to 10% of birth weight and return to birth weight by 2-3 weeks are commonly cited clinical criteria for acceptable initiation of breast-feeding. To explore these criteria, patterns of initial weight loss and return to birth weight were examined among 264 healthy, term, breast-fed infants. Primiparous mothers in a convenience sub-sample from a prospective study maintained infant feeding and elimination diaries during the first 2 weeks postpartum. Mothers received breast-feeding guidance and support. Infants were weighed naked twice during the 1st 2 weeks using the Sartorius integrating balance, and % weight change from birth weight was calculated. Milk ingestion was measured by change in infant weight before and after a feeding and milk yield was calculated in cc/hr since the infant last nursed.

Data were analyzed using SPSS/PC. Percent infant weight change from birth weight at the 1st visit (mean age = 5d) ranged from −14.3 to +15.3 (mean −1.79, median −1.80, S.D. 4.24). Weight loss exceeded 7% in 8.7% of infants. Among 236 exclusively breast-fed infants who were seen at a 2nd visit (mean age = 10d), 88.7% were above their birth weight. Pearson Product Moment Correlations were performed to ascertain the strength of association between % infant weight loss and selected infant feeding, elimination and milk intake variables. The timing of the first yellow "milk" stool was negatively correlated with % infant weight loss at the 1st visit (*r*= −.30, p=.000). A moderate correlation was found between % infant weight loss and total breastmilk intake measured at a feeding (*r*=.50, p=.000), as well as maternal milk yield calculated in cc/hr (*r*=.48, p=.000). Multiple regression analysis was performed to determine predictors of % weight loss at the 1st visit. Significant predictors were birth weight and maternal milk yield. The resultant equation (*F* [9,128] 3.07, *P* = 0.0000) accounted for 36% of the explained variance.

These findings suggest that, with conscientious breast-feeding management, few infants lose >7% of birth weight or fail to regain their birth weight by 2 weeks. Thus, emphasizing the extremes in breast-feeding "rules of thumb" may not be appropriate. Further studies are warranted to establish definitive criteria to assess the onset of breast-feeding.

Appropriateness of Admissions to a Canadian Children's Hospital

K. R. Kowaleski and M. Li

Division of Emergency Medicine,
Department of Paediatrics,
Children's Hospital of Eastern Ontario, Ottawa

Universal health care coverage may result in meaningful differences in hospital utilization between the U.S. and Canada. We analyzed the rate of inappropriate admission (RIA) to CHEO through the use of the Pediatric Appropriateness Evaluation Protocol (PAEP), a set of objective, diagnosis-independent criteria. We also examined variables that may have influenced this rate. The extent to which potential admissions that would have qualified as appropriate were diverted to the emergency room (ER) holding unit (HU) was also determined.

All non-psychiatric admissions every 12th day in 1989 was retrospectively reviewed. The primary rater was a medical student; a pediatric fellow also reviewed half the charts. The criteria are brief and straightforward; we believed a relatively inexperienced individual could use them reliably. The fellow's results were used to determine interrater reliability.

786 admissions were reviewed, 380 by both raters. 60.1% were male; median age was 4y. Classification by source was: 46.8% ER, 33.5% elective (L), 16.0% urgent (U) and 3.7% neonatal (N). 53.6% were admitted to a medical service, 46.4% surgical.

Overall RIA was 21.3%; however, RIA varied substantially depending on source: N 3.4%, ER 7.1%, U 33.3%, L 37.3% (p<.001). Sex (males 18.7%, females 25.2%; p<.05) was the only other variable demonstrating significant effect on overall results. Age, stay <1 day, day of week, season of year did not. For ER admissions, physician (full-time ER 2.4% vs. other 13.9%), medical (4.8%) vs. surgical (11.8%), and distance from home (<20mi 5.5%, >20mi 13.3%) were of significance (p<.05).

The most common reason for inappropriateness for L was premature admission; for U and ER, inpatient care unnecessary for tests/treatment given. 107 patients admitted to HU met appropriateness criteria. Between raters, general agreement was 93.4%, kappa=0.82, demonstrating high interrater reliability.

RIA at CHEO compares well with that of U.S. pediatric hospitals reported in the literature. We found ER RIA to be especially low. Overall RIA could be lowered by better timing of L admissions and/or having U admissions screened in the ER.

Parental Time and Expenses for Diabetes Care

G. E. Dougherty, A. Schiffrin, and L. Ball

Departments of Pediatrics and Epidemiology and
Biostatistics, McGill University, Montreal, Quebec

Parental time and out of pocket expenditure in the first month after diagnosis of childhood type I diabetes mellitus were measured as part of a randomized trial of traditional (T) versus comprehensive ambulatory care (CAC). Patients in the CAC group were discharged after stabilization of acute metabolic complications (0-5 days) and teaching and insulin adjustment were accomplished at home by a visiting nurse practitioner. Patients in the traditional group were admitted for 2 to 8 days to titrate insulin requirements, complete a formal educational program and allow for adjustment in the family.

The families' out of pocket expenses, parental time devoted to diabetes and time lost from work in the first month were collected via a telephone administered questionnaire supplemented by direct interview.

Mean total parental time expenditure was 144.6 hrs for the traditional group (N=15), and 101.9 hrs for CAC parents (N=18), (T=2.07 P=.047). The main differences occurred in the first 11 days when "T" parents spent a mean of 115.8 hrs at the hospital or providing direct care vs 74.9 hrs for CAC parents (T=2.40, P=.023). Time lost from work did not differ significantly and was 28.9 hrs vs 27.0 hrs, for T vs CAC.

Total out of pocket expenses for transportation, meals, child care, medical supplies and miscellaneous expenses were $350.68 vs $317.42 with the difference mainly due to transportation, neals and child care, T vs CAC, $123.76 vs $71.03 (T=2.32, p=.027).

Short term medical outcomes did not differ significantly in the wo groups. HbA1c's at 3 months were 5.40 vs 5.76% for T vs CAC.

Traditional care occupied more parental time and was more costly to families than comprehensive ambulatory care.

Simethicone in the Treatment of Infant Colic

T. J. Metcalf, T. G. Irons, L. D. Sher, and P. C. Young

Willow Creek Pediatrics, Salt Lake City, Utah;
East Carolina University, Greenville, NC;
Pennisula Allergy and Pediatrics,
Rolling Hills Estates, Calif;
and University of Vermont, Burlington

Simethicone, an antiflatulent, has been used by parents in the treatment of infantile colic for a number of years, on the advice of pediatricians, friends, or relatives. The authors designed a multicenter, randomized, double-blind, placebo-controlled, crossover trial to test the efficacy of Simethicone in infants with symptoms of colic, using a commonly accepted definition of the disorder. Eighty-three infants from three centers formed the data base. Each infant was randomly assigned to receive either simethicone or placebo for a one week treatment period followed by the opposite agent for a second treatment period. A total of 166 treatment periods were evaluated in 83 infants. Fifty-three percent of the treatment periods resulted in improvement compared to baseline; in 22% symptoms worsened, and in 24% no change was noted. The likelihood that an infant would improve, stay the same, or worsen during a treatment period was the same whether the infant was receiving simethicone or placebo (no significant difference by ANOVA). No difference could be shown even when infants with "gas-related symptoms" (by parental report) were evaluated as a group. We conclude that simethicone is no more effective than placebo in the treatment of infantile colic.

Tympanic Membrane Thermometers: Caveat Emptor

M. Nypaver, E. Zieserl, B. Nachtsheim, and A. T. Davis

Department of General and Emergency Pediatrics,
Children's Memorial Hospital, Chicago, Ill

Temperature (temp) measurement is integral to the evaluation of pediatric patients visiting the emergency department (ED). Glass and electronic thermometers are slow, cumbersome and uncomfortable for children. If reliable, the Tympanic Membrane Thermometer (TMT) offers a rapid, noninvasive alternative to the problem of temp measurement in children. Results of previous studies with the TMT are contradictory due to study design flaws. We hypothesized that the TMT yields a reliable measure of temp in children. In this prospective, comparative study we sought to: 1) determine the reliability of the Firstemp TMT to detect fever compared to our current standard, the IVAC digital thermometer, and 2) to determine if reliability was affected by patient age or range of temp. 1959 children of all ages were enrolled from the Children's Memorial Hospital ED during 2 months in 1990. Bilateral TMT temps were taken in all patients (pts) in addition to oral (ORL)-IVAC and/or rectal (REC)-IVAC temps depending on age and ability to cooperate. All temps were taken by ED nursing staff. Findings of cerumen, otitis media, perforation, myringotomy tubes, and foreign bodies were noted. Fever was defined as IVAC temp ≥ 38.5°C.

RESULTS: 1040 pts had ORL-IVAC temps, 939 pts had REC-IVAC temps and 23 pts had both. Mean difference (diff) between right and left ears = 0.005°C±0.45°C, (r=.88). For febrile children, mean diff between TMT and REC-IVAC = −0.35°C±0.47°C (r=.87); between TMT and ORL-IVAC = −0.13°C±0.54°C (r=.79). Although correlation was good, 28% of children with fever had normal TMT temps. The TMT underestimated IVAC temps more in febrile pts than nonfebrile pts (mean diff=0.44°C vs. 0.31°C, p<.001, t-test) regardless of age.

CONCLUSIONS: The Firstemp TMT is not a reliable indicator of fever in children due to its imprecision and significant variability; it missed almost 30% of children with fever and performed worse at higher temperatures. Age did not contribute to TMT performance. The Firstemp TMT should not replace electronic digital thermometers.

Over-the-Counter (O.T.C.) Medication Use in Children With Colds—a Critical Appraisal

M. B. H. Smith and W. Feldman

Department of Pediatrics,
University of Ottawa (Ontario)

Previous review articles on the use of OTC cough and cold medications in children have been inconclusive. Despite the lack of firm evidence supporting their use, these substances are present in most homes and continue to be a common cause of accidental ingestion in young children. In order to demonstrate a greater good than harm, these products must be shown to be effective for the symptomatic relief of the common cold in children. Our objective was to critically evaluate the medical literature to determine what medications have been shown to be effective in controlled trials and particularly their evaluation in children.

All relevant citations from January 1950 to November 1990 were categorized into six groups and given a scientific validity score based on the representativeness of the subjects, treatment design and objectivity of outcome measures. Those articles scoring over 70% were included in the final synthesis. 50 studies were analyzed in detail. Interrater reliability was good (weighted Kappa = .80).

No. of studies and mean scientific validity score (%)

	Supporting Use	Not Supporting Use
Adult Studies		
Antihistamines	3 (79)	6 (83)
Decongestants	4 (77)	1 (70)
Antitussives	-	-
Expectorants	-	1 (77)
Anticholinergics	1 (100)	1 (92)
Combinations	6 (85)	1 (92)
Child Studies		
(Age > 5 Years)	1 (85)	1 (77)

We conclude that some OTC cold medications have been demonstrated to reduce the symptoms of the common cold in adults including smokers. Only 2 studies involved children (5 - 12 years) and their results were diametrically opposed. No controlled trials have been done in children under 5 years. Since this is the age group most likely to use or ingest excessive amounts, these products should be considered experimental for young children.

Intermittent Versus Continuous Amoxicillin Prophylaxis for Infants and Children With Recurrent Otitis Media With Effusion

S. Berman, R. Nuss, R. Roark, C. Huber-Navin, K. Grose, and M. Herrera

Department of Pediatrics, University of Colorado
Health Sciences Center, Denver

The efficacy of continuous (C) amoxicillin prophylaxis was compared to intermittent (I) prophylaxis with cold symptoms in a randomized single blinded prospective clinical trial. Eighty-four patients (31 infants and 53 children) who experienced three episodes of otitis media with effusion (OME) in the 6 months preceding entry into the study were randomized to I amoxicillin and 89 patients (38 infants and 51 children) to C amoxicillin. For infants less than 12 months of age, the overall OME incidence rate per 120 days at risk was 1.18 for I amoxicillin versus 1.25 for C amoxicillin. C amoxicillin was associated with a lower OME incidence rate for infants enrolled during the winter months while I amoxicillin had a lower incidence rate for infants enrolled during the remaining months. For children 1 year of age or older, the overall incidence rate per 120 days at risk was 0.70 for I versus 0.43 for C amoxicillin. During winter months the incidence of OME for children on I amoxicillin was 3.5 times higher than the rate for children on continuous amoxicillin (0.80 versus 0.23).

	Intermittent Amoxicillin Entered During			Continuous Amoxicillin Entered During		
	All Year	Winter	Non-Winter	All Year	Winter	Non-Winter
Total Patients	84	37	47	89	35	54
Infants <12 mos.	31	16	15	38	10	28
Children >12 mos.	53	21	32	51	25	26
Incidence Rate						
Total Patients	0.87	1.10	0.70	0.74	0.46	0.97
Infants <12 mos.	1.18	1.52	0.85	1.25	1.15	1.30
Children >12 mos.	0.70	0.80	0.64	0.43	0.23	0.68

The results support treating infants and children with continuous antibiotic prophylaxis during winter months and with intermittent prophylaxis at other times.

Duration of Positive Streptococcal Throat Cultures After Initiation of Antibiotics

L. W. Snellman, H. J. Stang, J. M. Stang,
D. R. Johnson, and E. L. Kaplan

Departments of Pediatrics, Group Health, Inc, and
University of Minnesota,
White Bear Lake and Minneapolis

Recommendations differ concerning when, after initiating antibiotics, a patient with group A streptococcal (GAS) pharyngitis may return to school with diminished risk of transmission. We are aware of no prospectively collected data which completely address this issue. This study was undertaken to determine the period of contagiousness as manifested by positive throat culure.

Children (4-18 years) with pharyngitis associated with the presence of GAS were enrolled. They received either oral penicillin V (OP), oral erythromycin estolate (OE), or intramuscular benathine penicillin G (BPG). During three home visits in the 24 hours following initiation of antibiotic therapy, additional throat ultures were obtained and clinical signs and symptoms were recorded. Serum samples were obtained at enrollment and at 4 weeks for anti-streptolysin O (ASO) and anti-DNAse B titers.

Of 47 children enrolled, 39 (83%) became culture negative within 24 hours. For these 39 patients, the mean time to first egative culture was 17.6 hours. Neither time to conversion to egative nor positivity of any single culture could be predicted y clinical signs or symptoms. There was no difference in mean me to first negative culture between the OP and BPG groups. However, 75% of patients who failed to convert to negative within the first 24 hours were in the OE group (OP: 1/17 [5.9%]; PG: 1/15 [6.7%]; OE: 6/15 [40%]). There was also no difference in either time to conversion to negative or the positivity of culture t 24 hours between those who had a rise in ASO and/or anti-NAse B titers and those who did not.

These data suggest that children with GAS pharyngitis treated ith penicillin have reduced communicability and may usually turn to school after 24 hours of therapy. These data further uggest that erythromycin may be less effective.

DEVELOPMENTAL AND BEHAVIORAL PEDIATRICS

School Outcomes of Children With Asthma

M. G. Fowler, R. Garg, and M.G. Davenport

Office of Analysis, National Center for
Health Statistics,
Hyattsville, Md, and
Clinical Trials Branch,
National Heart, Lung, and Blood Institute, Bethesda, Md

Children with asthma are at increased risk for school problems. Data from the 1988 U.S. National Health Interview Survey on Child Health, a representative national cross-sectional survey, were used to determine national estimates of school outcomes for children reported to have asthma (CWA) compared to children without current conditions (CWNOCC). Among the 10,362 survey children in school grades 1-12, families reported that 536 (5%) had had asthma in the previous 12 months; prevalence varied little by demographic factors although blacks had slightly higher rates than nonblacks.

Regarding school outcomes, mean days absent were 7.5 days for CWA versus 2.5 days for the CWNOCC group; twenty percent of CWA missed 11 or more school days in the previous 12 months versus only 2.5% for CWNOCC. Seventeen percent of CWA had ever repeated a grade compared to 15% of CWNOCC, and 9% CWA were reported to have learning disabilities compared to 5% of CWNOCC. Thirty percent of CWA were reported to have some activity limitation, compared to only 2% of CWNOCC. Using logistic regression to control for demographic factors, CWA had similar (OR = 1.3) risk of grade failure but 1.7 times the risk of learning disability compared to children without chronic conditions. For CWA, activity limitation was an important predictor of school outcomes: those children with activity limitations were 2.5 times as likely to repeat a grade, and 5 times as likely to have a learning disability, compared to CWA without limitations. Likewise, CWA with activity limitations averaged 11 days absent versus 7 days for those with no limitations. These national data underscore the importance of evaluating children with asthma for special academic needs and also suggest that optimal treatment to reduce activity limitations among asthmatic children may facilitate their school functioning.

Homage to a Clinical Observation: Empirical Support for Wessel's Definition of 'Colic'

R. G. Barr, A. Rotman, J. Yaremko, D. Leduc,
T. E. Francoeur, J. Desilets, and R. DuBerger

Department of Pediatrics, McGill University,
Montreal, Quebec, and
Montreal Children's Hospital

To provide the first controlled empirical description of the clinical features of colic, 38 infants whose mothers considered crying a problem ("colic") and 38 age, sex, parity and ethnicity pair-matched controls were observed at home 10 min. before and after an evening feed and by mothers for 7 days with pre-validated diaries. Measures included (1) duration and frequency of cry and fuss (C/F), (2) crying after feed, (3) distention (fat free abdominal girth), (4) temperament ratings, and (5) 8 parent ratings of cry quality. Following Wessel (1954), each "colic" infant was classified by number of days/wk of C/F duration ⩾3 hrs/day. The distribution showed 2 peaks at 0 and 3 days/wk. Colic infants with C/F ⩾3 hrs/day for ⩾3 days/wk were called *Wessel's* Colic (WC), the others *Non-Wessel's* Colic (NWC). Groups were compared by ANOVA (post hoc Tukey) or χ^2 analyses.

Neither crying after feed nor distention differed between groups. WC infants cried over twice as long as *both* NWC and Controls (4.1 vs. 1.7 and 1.7 hrs/day; F [2,70] = 37.1, P<.001) but re was no difference in frequency (7.8 vs. 5.7 vs. 7 bouts/day; 1.4, P=.25). The same pattern occurred with Temperament: were significantly more negative than NWC and Controls 5.2 vs. −0.7 and 1.3: F[2,65]=7.8, P=.001). In contrast, there s no difference before or after feeds on 7 of 8 cry ratings except the "sickness" rating. It *increased* after feeds for *both* WC *and* VC infants (3.8 and 3.2) compared to cries before feed (2.3 and , respectively) and controls (1.8 before and 1.7 after feed: oup × feed F[2,45]=3.5, P=.04).

ONCLUSION: In infants presenting with problem crying, re are probably 2 groups: (1) "Wessel's" colic with longer cry ration and negative temperament, and (2) "non-Wessel's" ic with cry duration and temperament similar to controls. Cry qually likely after feeding in all infants and quality is similar. wever, if seen as indicating "sickness," crying may be a com- int in both groups.

eventing Disruptive Night Waking In Infancy: n Effective Primary Care Intervention

Adair, H. Bauchner, B. Philipp,
Levenson, and B. Zuckerman

epartment of Pediatrics,
oston (Mass) City Hospital,
oston University School of Medicine

Approximately 25% of young infants wake at night. The pur- se of this study was to implement and evaluate a brief inter- ntion to prevent disruptive night waking. Parents were en- lled as they sought care at the Lahey Medical Center, rlington, MA. The control group was enrolled at the 9 month sit, the intervention group at the 4 month visit. For the inter- ntion parents: (1) were advised to place their infants partially vake in the crib at bedtime starting at 4 months, and (2) com- eted a daily routine chart prior to the 6 month visit then re- ewed it with the MD. Parents in both groups completed an tcome questionnaire when their children were 9 months old. ll contacts addressed feeding and sleeping in order to obscure e purpose of the study.

128 of 172 (74%) invited infant-parent pairs comprised the con- ol group and 164 of 222 (74%) the intervention group. The ma- rity of families were white (97%), well-educated (66% parents llege graduates) and financially secure (83% yearly income > 30,000). The groups were also similar with regards to infant age, ender, number of siblings; parental age, marital status; and fac- rs shown to be related to night waking: current breast feeding, umb/pacifier sucking and maternal isolation.

Infants in the intervention group averaged 2.5 wakings/week ersus 3.9 in the control group (p=.02), a 36% reduction. Fre- uent night waking (> 7 wakings/week) occurred in 14% of in- ervention infants versus 27% of control infants (p=.01), a 48% eduction. We conclude that with this intervention pediatricians an help parents prevent disruptive night waking in young in- ants.

dentifying Sources of Discrepancy Between Pediatricians' Diagnoses nd the Child Behavior Checklist

S. M. Horwitz, P. J. Leaf, J. M. Leventhal,
B. W. C. Forsyth, and K. N. Speechley

Departments of Epidemiology and
Public Health and Pediatrics,
Yale University School of Medicine,
New Haven, Conn

Previous research indicates that when pediatricians' diagnoses of psychosocial (PS) problems are compared to those from a structured assessment tool such as the Child Behavior Checklist (CBCL), there is little agreement on which children have PS problems. The purpose of this study was to measure disagreement between the CBCL and clinicians and identify sources of conflict. We hypothesized that issues such as clinician's knowledge of a child, type of visit, and differences in diagnostic thresholds between clinicians and the CBCL may account for the discrepancies. We investigated this in a random sample of 19 out of 23 (83%) pediatric practices in New Haven, CT. We collected PS information from physicians using a 12-category checklist based on a WHO-sponsored primary care classification system.

Of the 2006 children 4-8 years visiting these practices, 1886 children and their families (91%) participated. At entry, 52% were 4-5 years, 50% were male, 80% were white, and 59% were visiting for acute care.

Pediatricians identified 515 children (27%) with ≥1 PS problems while the CBCL identified 322 children (17%). Overall, pediatricians and the CBCL disagreed on 29% of the children. When we examined disagreement for that group of children in which the hypothesized methodological problems had been corrected [i.e., for well-child or follow-up visits to the usual clinician who knew the child well (N=485)], the disagreement rate was similar (36%). Within the 485 children, we next examined the reasons for these discrepancies. In 83/155 children (54%) where the pediatrician but not the CBCL indicated a PS problem, children had CBCL scores of 50 or more, indicating many problem behaviors. These CBCL scores were not high enough to meet the diagnostic cutoff. In children with CBCL scores less than 50 (N=72), pediatricians and the CBCL identified the same problem in 34 children (47%). Of the 25 cases where the CBCL but not the physician indicated a problem, 7 (28%) had a past problem indicated by the clinician.

We conclude that previously reported discrepancies are largely due to differences in diagnostic thresholds between clinicians and the CBCL.

Understanding the Development of Failure to Thrive in a Low Birth Weight, Preterm Cohort: A Prospective Study to Age Three

P. H. Casey, K. Kelleher, R. H. Bradley, M. Swanson,
L. Whiteside, S. Pope, and K. Barrett

Department of Pediatrics, University of Arkansas
for Medical Sciences, Little Rock

The development of Failure to Thrive (FTT) was assessed in a prospective study of low birth weight (LBW) preterm (PT) infants to avoid methodologic problems of previous retrospective research. 985 infants (birth weight ≤2500 gm, gestation age ≤37 wks) were recruited in the nursery in a 8 site collaborative research program. All infants received routine follow up care at standard intervals, and a broad range of infant, parent, and environmental data were collected in the nursery and at 40 wks, 4, 8, 12, 18, 24, 30, and 36 mos gestation corrected age (GCA). Clinicians were instructed to utilize a standard definition using growth data; in addition, a computer model was employed to assess normal interval growth. One hundred fifty six (156) infants met both criteria by 36 mos and were considered FTT. 144 infants were excluded as they met only 1 criteria. Bivariate analyses compared all independent variables collected from 40 wks to 30 mos GCA between 156 FTT and 685 non-FTT infants. Of all the maternal and environmental variables, only the 12 mos household density and the quality of home environment as measured by the total HOME Inventory and its Responsivity, Play Materials, and Involvement subscales differentiated the groups (p≤.01). FTT infants were rated lower by their mothers on the 12 and 24 mos Health Rating Scale (p<.001), had more chronic conditions at 12 and 24 mos (p<.001), and were more likely to be judged suspect or abnormal on the neurologic examination at all clinical visits (p<.01). The FTT infants scored lower on the Bayley MDI and PDI at 12 and 24 mos GCA (p<.002). There were no differences in neonatal health, infant temperament, family stress, support, SES, or maternal mental health, knowledge, or I.Q.

In this large cohort of LBW, PT infants followed longitudinally, several medical characteristics of the child, along with the quality of their home environments, differentiated the group of children with FTT from those without FTT. These results should assist in the development of identification and intervention strategies regarding FTT in LBW, PT infants.

The Mental Health of Children Placed With Relatives

H. Dubowitz, V. Tepper, S. Zuravin, and S. Feigelman

Department of Pediatrics,
University of Maryland Medical School, Baltimore

Placement with relatives is generally the first option of public agencies seeking substitute care for children, mostly due to child abuse or neglect. This is the first evaluation of the prevalence and treatment status of mental health problems of children in this type of foster care.

METHOD: Subjects were *all* 524 children living in relative placements in Baltimore in April, 1989. Data were gathered from medical records, mailed questionnaires to health care providers, parents, relative caretakers, caseworkers and the adolescents, and a clinical assessment involving standardized measures and interviews.

RESULTS: Only 58% of the children aged 0-5 years passed the Battelle developmental screening test. The median percentiles on a test of cognitive functioning were far below normal for the older children. Forty-six percent of the children had clinically significant behavior problems on the Achenbach CBCL; 32% were depressed. Only 27% of the children, mostly in the 0-5 age group, had no mental health diagnosis. Fifty-eight percent had 1-2 problems and the remainder had >2. Many of these problems had not been identified or were not being addressed and 38% of the children clearly needed follow-up.

Increased mental health problems were associated with older age at placement ($p=.001$), increased duration of placement ($p=.001$), older current age ($p=.001$), and male gender ($p=.0001$). Increased problems were also associated with previous abuse ($p=.01$), the caretaker having made more contact with the caseworker ($p=.01$) and receiving more services ($p=.003$). Children with increased problems were more likely to be placed with older relatives ($p=.01$), in homes with more children ($p=.01$), and viewed by the relative as "difficult".

IMPLICATIONS: Children placed with relatives appear to have substantial mental health problems, many of which are not being addressed. Their problems are similar to those of other foster children, but appear to be greater than those of poor children and the population in general. Families, health professionals, and the child welfare system should address these needs.

Child Rearing Practices and Nursing Caries

J. R. Serwint, R. Mungo, V. Negrete,
M. E. Guzman, and B. M. Korsch

Departments of Pediatrics
and Pediatric Dentistry,
University of Southern California
School of Medicine, Los Angeles,
and Children's Hospital of Los Angeles

In the dental literature, nursing caries are attributed to factors such as bottle feeding past 12 months of age, night time bottles and parental inability to say no to their children. We conducted a cross-sectional study in a pediatric residents' clinic to determine which factors may be predictive of nursing caries.

Caregivers of children aged 18 to 36 months were interviewed to determine feeding practices, dental health behavior, limit setting and sleep issues after which the children's teeth were examined. Of 110 children enrolled, 22 (20%) were found to have nursing caries.

Children with caries were older, and compared to children without caries, were more likely to have younger siblings, 69% vs. 35% ($p = .03$), lower maternal educational level, 8.6 vs. 11.2 years ($p = .02$), and mothers with 8 or more cavities, 55% vs. 19% ($p = .002$). At the time of the interview, 50% of those who had caries and 72% of those who did not were still taking the bottle ($p =$ ns).

More infants in the caries group had been breast fed, 77% vs. 46% ($p = .02$), although length of breast feeding was similar, 5.3 vs. 6.3 months. Fewer children with caries drank tap water, 27% vs. 54 % ($p = .05$); there were no differences in topical fluoride use, tooth brushing practices or visits to the dentist.

Ninety-five percent of children with caries and 97% without had taken bottles while sleeping. There were no differences in number of daytime or night time bottles, or use of a pacifier or security object. There were also no differences reported in night waking, cosleeping, or parental report of difficulty in saying no to the child or difficulty disciplining the child. However, children with caries were more likely to specifically wake for a bottle at night, 64% vs. 36% ($p = .05$), and their mothers were more likely to feel that the bottle helped motivate the child to do things, 58% vs. 23% ($p = .02$).

These data fail to substantiate a straightforward relationship between child rearing practices and nursing caries and suggest that well designed prospective studies are needed to clarify the etiology of early caries.

Detecting Family Violence in the Context of Pediatric Continuity Care

L. S. Wissow, M. E. H. Wilson, and D. Roter

Johns Hopkins Medical Institutions, Baltimore, Md

Family violence is a common but frequently undisclosed contributor to problems with child behavior and development. We compared 3 methods of detecting family violence in the context of pediatric continuity clinic visits: 1) prior to a scheduled visit with their child's pediatrician mothers completed an adaptation of the Conflict Tactics Scale (CTS) (Straus, 1979), a measure of violent behavior among any members of the child's family; 2) the visit was audiotaped and coded by a research assistant who documented disclosures of corporal punishment, which often occurs in conjunction with violence among other family members; 3) at the end of the visit the physician, without knowledge of the mother's response to the CTS, rated the chance that there might be a problem with interpersonal violence in the family. The study took place in an inner city hospital's residents' continuity clinic. Fifty-seven mothers were systematically enrolled, representing visits to 19 PGY2 and PGY3 pediatric residents.

Nearly half (26/57) of the mothers gave positive responses to the CTS (answered "at least once or twice in the past year" to one or more of the last five items, including "kicked, bit or hit with a fist" through use of a weapon). During 15 of the 57 visits (26%) there was an explicit disclosure of corporal punishment. These 15 disclosures included labeling the child as "bad" or a cause of extreme parental distress (4), mentioning the threat of a beating as a means of controlling the child (2), and either describing a specific beating or striking the child in the exam room (6). Eight of the 15 disclosures were initiated by the mother, with the remainder coming in response to physician questions about behavior or discipline. Physicians rated 53 of the 57 families as having little or no chance of experiencing a problem with interpersonal violence, including 13 of the 15 families that had disclosed or demonstrated corporal punishment during the preceding visit. Neither disclosure of corporal punishment nor physician prediction was a sensitive or specific predictor of a mother's response to the CTS. We conclude that instruments such as the CTS are important parts of the effort to help physicians become aware of the broader range of intrafamilial violence experienced by children.

Depression and Role Satisfaction in Mothers of Toddlers

A. L. Olson and L. A. DiBrigida

Department of Maternal and Child Health,
Dartmouth Medical School, Hanover, NH

Maternal depression is an important problem for pediatricians caring for toddlers since it can affect children's behavior and development. Work can affect the mental health of mothers in a positive or negative manner. Mothers may find themselves against their wishes in a position of working or staying at home which may influence their mental health. Pediatricians have freuent contact with mothers during the toddler year. We gathered ata on the prevalence of depression and its association with mployment. We hypothesized that mothers who are satisfied with their current role, whether at home, or employed, will have ess depression than mothers who are not.

To test this hypothesis we conducted a cross-sectional practice ased survey of maternal self reported symptoms of depression with 234 mothers of toddlers (12-24 mon.) at well child visits in wo community pediatric practices from the Dartmouth-Hitchcock Pediatric Practices Collaborative Research Group. Deression was assessed with a 20 item depression screening inentory, developed by Barrett, Oxman and Gerber and based on he Hopkins Symptom Checklist-90 for use in primary care pracce. It allows one to assess 3 levels of depressive symptomatology depressive mood, syndrome or disorder) with cut off levels on scale of 0 to 60 of ≥9, ≥14 and ≥19. It also allows a mean deression score to be calculated. Data was obtained on parents' ocioeconomic status, hours worked, and whether the mother was satisfied with her current role of being at home or employed.

Depressive symptoms were present to some degree in 52% verall. This included depressive mood only in 10%, depressive yndrome in 25%, and depressive disorder in 17%. Mean scores or depression were somewhat better for working than nonworking mothers (11.3 work vs 13.2 home, t-test, p = .02) but the 42 mothers who were disatisfied with their current roles had much igher depression scores (20.5 dissatisf. vs 10.3 satisf., t-test, = .002). The association of satisfaction and depression with maernal education or employment, parental SES, parity and maernal age were also examined.

These results indicate that the majority of mothers of toddlers in a pediatric practice were depressed to some extent. Role satisfaction was more important than employment status in depresive symptoms. We need to give more careful attention to these ssues during toddler visits.

Maternal Attitudes As Predictors of nfant Feeding Decisions

. I. Dungy, J. Christensen-Szalanski,
M. Losch, and D. Russell

Department of Pediatrics,
he University of Iowa, Iowa City

The rate of breast feeding among women in the United States has been declining since 1982. In order to develop intervention trategies to reverse the downward trend it is important to deermine the factors influencing maternal infant feeding deciions. Most previous studies have evaluated various socio-demoraphic characteristics to predict infant feeding behavior. The resent study reports an easily constructed attitude profile that s closely correlated with maternal infant feeding behavior. 219 women were interviewed within 48 hours of birth to determine hose factors most closely associated with the infant feeding deision. Socio-demographic characteristics including age, ethnicty, education, family income and parity were obtained for each espondent. In addition, maternal attitudes concerning infant eeding were assessed through the use of a multi-attribute utility MAU) scale composed of ten topic areas. Five topic areas (nurition, cost, maternal appearance, pleasure and well-being) adressed selected aspects of breast milk and infant formula (product dimension). The remaining 5 areas (parental role, physical loseness, infant intake, feeding ease and night feeding) focused n breast feeding and bottle feeding (process dimension). A disriminant function analysis using socio-demographic variables previously shown to be correlated with maternal feeding deciions was only marginally able to discriminate breast feeding rom bottle feeding women (kappa = .30). However, a discriminant function analysis based on the MAU was able to identify orrectly nearly all mothers' infant feeding choices (kappa = .90). Thus, the attitude profile was significantly better ($p < .001$) in predicting feeding choices than were socio-demographic charcteristics. The results indicate that the MAU provides easily obtained information useful in predicting maternal infant feeding decisions.

The Feasibility and Utility of Psychosocial Screening in a Pediatric Clinic

K. J. Kemper

Department of Pediatrics,
University of Washington,
and Harborview Medical Center, Seattle

Screening for psychosocial risk factors which affect parenting has been limited by lack of a structured approach. The purpose of this study was to assess the feasibility and utility of a self-administered questionnaire in screening for risk factors for poor parenting; eg. substance abuse, history of parental abuse as a child, depression, self-esteem and social support. Questionnaires were offered to mothers bringing their children for routine care at an urban pediatric clinic from April 15-June 15, 1990. In addition to routine medical history, the questionnaire included standard screening questionnaires on psychosocial conditions, eg. Cyr's two-item screening test for alcoholism, Rosenberg's Self-Esteem questionnaire, and the Screening Instrument for Depression. Charts were reviewed for 114 children whose mothers completed part or all of the questionnaire and 117 randomly selected children whose mothers had not. Mothers who filled out questionnaires were similar to mothers who did not in terms of maternal age (x = 25 years) and education (x = 11.5 years), payor status (Medicaid = 70%) and the frequency with which psychosocial problems were noted on the chart (eg. drug problem in the home in 24% vs. 22%). For those who returned questionnaires, the response rate, even for sensitive questions was high (eg. household income, 85%; maternal drug use, 97%; and domestic violence, 89%). Overall, the questionnaire identified significantly more children with one or more of the risk factors for poor parenting than the chart did (64/114, 56% vs. 43/117, 37%, P = 0.005). For example, parental history of abuse as a child was noted on 41 questionnaires vs. 3 charts (P<0.001). Self-administered questionnaires addressing psychosocial risk factors are feasible, yield important information for family health and parenting, and should be considered as part of routine intake procedures in pediatric clinics, especially those serving high-risk populations.

Developmental Delay Among Homeless Children

B. P. Dreyer, C. D. Courtlandt, A. H. Fierman,
M. Arbel, G. Benincasa, C. Squittieri,
L. Palevsky, and N. Mann

Department of Pediatrics,
New York (NY) University School of Medicine

To determine whether young homeless children are at risk for developmental delays, we studied children residing in a shelter for single homeless mothers and their children. Medical, social, and family histories were obtained, and the Revised Gesell Developmental Examination and the Denver Developmental Screening Test (DDST) were administered to all children 15-30 months of age with no known developmental problems (N = 25). Each item on the Gesell was scored by two observers. Developmental ages were determined by a third researcher blinded to the age, sex, race, and performance of the child. All families were Hollingshead SES Group V, medicaid eligible, and receiving AFDC benefits. 20 (80%) mothers failed to complete high school. 16 (64%) fathers were arrested for a violent or drug-related crime. Only 3 mothers admitted to drug use.

The mean (±SE) developmental quotients (DQ) on the sections of the Gesell were as follows: adaptive 77.6 (1.6); fine motor 79.4 (1.9); language 77.1 (1.8); gross motor 95.9 (2.2); personal-social 93.5 (2.4). Mean DQs for the homeless children were compared with those of the 15-36 month-old subset of the 1980 Gesell sample with a maternal education level of high school or less. Homeless children scored significantly lower on all sections (adaptive, fine motor, language p<.001; gross motor p<.05; personal-social p<.01). 10/25 (40%) homeless children failed the Gesell. An additional 11/25 (44%) scored in the questionably abnormal range. After controlling for sex, race, birth weight, gestational age, birth order, child's current age, chronic/recurrent illness, maternal age and educational level, family size, and paternal arrest, a duration of homelessness of greater than four months was significantly associated with lower scores on the Gesell adaptive, language, and fine motor schedules (p<.05). All children passed the DDST; one child had a questionable result.

We conclude that young homeless children exhibit significant which may influence their mental health. Pediatricians have fredelays in development. Longer duration of homelessness was associated with more extreme delays. The DDST was insensitive in identifying these delays. Effective developmental evaluation and intervention programs are indicated for young children residing in homeless shelters.

EMERGENCY MEDICINE
AND
CHILD ABUSE

The Failure of Tympanic Thermometry to Detect Fever Accurately in a Pediatric Emergency Department (PED)

C. Garabedian, R. Vinci, D. Dwyer, and H. Bauchner

Division of Pediatric Emergency Medicine,
Department of Pediatrics,
Boston (Mass) University School of Medicine
and Boston City Hospital

The presence of fever is an important finding in the evaluation of the pediatric patient. Tympanic thermometry (TT) is a new technique that assesses body temperature by measuring infrared radiation from the tympanic membrane. The purpose of this report is to assess the accuracy of TT in the PED.

Following an inservice program, nurses performed both TT and rectal or oral temperatures in 845 consecutive patients who presented to the PED. The majority were male (53%) and black (65%). We identified a discrepancy between TT and rectal temperature in 6% (15 of 239) of children < two years of age. Using temperature ≥ 100.4°F in children ≤ 3 months of age as the clinical marker of serious illness, 1 of 57 children was afebrile by rectal temperature, but had a temperature by TT. Using temperature ≥ 102°F in children between 3 and 24 months of age as a clinical marker of serious illness, 14 of 209 children may have had their clinical management changed if TT alone was used, with 7 potentially having additional studies (such as a CBC and blood culture) and 7 potentially less studies. We found no discrepancies between TT and rectal temperatures, when rectal temperatures were ≤ 100°F (N = 126) in children between 3 and 24 months of age.

We conclude (1) TT is not accurate in assessing febrile children, and that in a substantial number of patients, clinical management may be different if TT alone is used to assess temperature, and (2) when TT indicates, in children between 3 and 24 months of age, that the temperature is ≤ 100°F no rectal temperature is necessary.

Refinement of the Child Vulnerability Scale

B. W. C. Forsyth, P. J. Leaf,
S. M. Horwitz, and J. M. Leventhal

Departments of Pediatrics and
Epidemiology and Public Health,
Yale University School of Medicine,
New Haven, Conn

Parents' perceptions of their child's vulnerability can affect both their child's psychological development and use of health are. The Child Vulnerability Scale (CVS) has previously been sed to demonstrate factors associated with increased percepons of vulnerability. To date, there has been no validation of the CVS.

By definition, two major factors contribute to perceptions of vulnerability: prior fears that a child might die; and the presence of severe medical illness. In this research, association with these two factors is used to refine the CVS.

Children, ages 4-8 yrs, were enrolled in a community-based study and 1095 mothers completed interviews which included the 12-item CVS and questions about the two factors. Mothers of 226 children (21%) reported that they had feared their child might die (factor A) and 45 children had a severe medical illness (factor B).

Four items were deleted from the CVS because item scores were not significantly different for subjects with and without the two factors. Changes were made in the scoring of the new 8-item scale and comparisons made between new and old scales. Using the new scale, 22.1% of children with factor A were categorized as vulnerable vs. 7.5% without factor A (Risk ratio 2.9, P<.001); 37.8% of those with factor B were vulnerable vs. 3.1% without factor B (RR 12.1, P<001). Using the old 12-item scale the RRs for these two comparisons were only 2.0 and 5.4 respectively. Using the new scale, only 1.9% of those without either factor were categorized as vulnerable. By comparison, 13.3% of those with factor A alone (RR 6.9), 33.3% of those with factor B alone (RR 17.2) and 42.8% of those with both A and B (RR 22.1) were categorized as vulnerable. Further analyses using the new scale confirmed previously reported associations with vulnerability.

Cocaine-Exposed Newborns in an Inner-city Community Hospital

A. Theodorou, T. Holtrop, J. Marshall, K. Meert, and A. Sarnaik

Children's Hospital of Michigan,
Wayne State University, and
Samaritan Health Center, Detroit

The prevalence of newborn cocaine-exposure has been estimated at 15% at inner city, tertiary care centers based on urine drug screens. We believe the problem is not limited to large medical centers, and initiated this study to evaluate the problem in a community hospital. We reviewed all the deliveries in 1987 (n = 1131) and identified 105 (9.3%) newborns with in-utero drug-exposure, the diagnosis made by urine drug screen and/or maternal history. Of these, 87 were exposed to cocaine either as the only drug or in combination with other drugs. Those exposed to cocaine alone (n = 73) were compared to a randomly selected group of non-drug-exposed infants born during the same time (n = 140). Dependent variables recorded include birthweight, Apgar score, presence of meconium staining, type of delivery, prematurity (<37 weeks), symptoms of tremors or irritability. The cocaine-exposed infants demonstrated lower birth weight (controlled for smoking), higher incidence of meconium staining, increased tremors and irritability, and a greater number of home deliveries (table).

	Birth Wt (grams)	Meconium Stained	Home Delivery	Tremors	Irritability
Cocaine	2677±439	30%	15%	51%	37%
Control	3024±564	11%	3%	16%	6%
p value	<.005	<.005	<.005	<.0005	<.0005

No significant differences were observed in the incidence of prematurity, c-section, or Apgar scores. Twenty-six (36%) of the cocaine-exposed infants had no observable symptoms. There were two deaths in the drug-exposed group. One infant died of SIDS at 4 mos. of age and another from an acute ingestion of cocaine at 5 mos.

We conclude that intra-uterine cocaine-exposure is a problem that can exist in a community hospital. The neonatal characteristics that we identified are consistant with the physiologic effects of cocaine on the fetus, placenta and uterus. Since a large number of cocaine-exposed newborns may remain asymptomatic, we recommend routine drug screening in high risk areas.

ediatric Emergency Medicine— tate of the Art

). J. Isaacman, R. B. Karasic, and H. W. Davis

epartment of Pediatrics,
Iniversity of Pittsburgh (Pa) School of Medicine

To assess the current practice of pediatric emergency care in ıe US, a questionnaire was mailed to the directors of all 240 mergency departments (EDs) affiliated with pediatric residency ·aining programs in the US. One hundred fifty-three (63.8%) rograms returned completed surveys, which comprised 32 uestions highlighting staffing patterns, ancillary services, clin- ·al issues, and resident education. Selected data are presented.

The mean annual ED census was 39,376; 6.5% of visits were ıtegorized as critical, 22.3% urgent, and 71.2% non-urgent. leven percent of patients were admitted to the hospital. During eak periods, non-urgent patients waited an average of 1.5 hours) be seen by a physician.

Twenty-two percent of programs provided 24 hour on-site cov- rage by a pediatric attending or fellow. Of the remaining pro- rams, the average daily on-site pediatric attending coverage was .3 ± 6.1 hours. Seventeen percent of programs utilized phy- ician assistants or nurse practitioners in the ED. During the first, econd, and third years, pediatric residents spent 4.8, 5.4 and 3.8 reeks in the ED, respectively.

The majority (88.1%) of EDs handled all levels of pediatric ·auma, had dedicated trauma teams (71.2%), employed social rorkers specifically assigned to the ED (62.9%), and had child buse teams (69.9%). Ninety-two percent of EDs had radio com- ıunications with pre-hospital care vehicles and 69.9% provided ıedical command for incoming pediatric patients.

Fifty-three percent of programs had a mechanism for ensuring elephone follow-up of worrisome patients, and 69.6% utilized system for ensuring feedback to the referring physician. Ninety- our percent of programs had a system in place for contacting atients with positive cultures; in most cases this function was andled by physicians. Seventy-five percent of programs pro- ided medical advice over the telephone.

These data highlight current practice patterns in EDs associ- ted with pediatric training programs and may assist in the de- elopment of practice standards for pediatric emergency care.

efervescence As a Guide to Resolution f Bacteremia ı Ambulatory Children

. Agre and L. R. Prieto

epartment of Pediatrics,
ollege of Physicians and Surgeons,
olumbia University, New York, NY

We wanted to determine whether presence or absence of fever orrelated with persistence or resolution of bactermia in children. acteremic children between the ages of 1 month and 19 years rere eligible for study. Every patient with a positive blood cul- ıre was recalled for evaluation and reculturing by a physician. rom 1986 to 1990, 95 bacteremic children were identified, 92 of rhom made return visits. Medical records were retrievable for 4 of the 92, and these form the study group. 79/84 children were reviously healthy. 70/84 were in the age range of 2 to 24 months. pathogenic organisms were isolated, of which the three most ommon ones were *Streptococcus pneumoniae* (69%), *Salmonella en- ritidis* (15%), and *Haemophilus influenzae* (5%).

5/84 patients had persistently positive blood cultures and were ebrile ($T>38^\circ$ C) at the time of the return visit. 79/84 patients had egative repeat blood cultures at the time of the return visit. Of ıese, 20/79 were febrile and 59/79 were not. No afebrile patient ras persistently bacteremic. Using Fisher's exact test a statisti- ally significant difference was found between the persistently nd resolved bacteremic patients with regards to fever $) = 0.002$). 2/5 persistently bacteremic patients were prescribed ntibiotics at the first visit and 3/5 were not. 58/79 resolved bac- eremic patients were prescribed antibiotics at the first visit and 1/79 were not.

We conclude that the majority of ambulatory bacteremic patients have resolution of their bacteremia whether they are treated with antibiotics or not. The presence of fever was not necessarily indicative of persistent bacteremia. However, the absence of fever was consistently indicative of resolved bacteremia.

Positive Effect of an Educational Intervention on Compliance With Universal Precautions in a Pediatric Emergency Department

L. R. Friedland, M. Joffe, and J. F. Wiley II

Emergency Medicine, Section of General Pediatrics,
St Christopher's Hospital for Children,
Philadelphia, Pa

We prospectively studied compliance with universal precautions by nurses and residents in our pediatric emergency department (ED), and then investigated the effect of an intensive educational intervention (lectures, written materials, posters) which stressed the need for universal precautions in the ED. The cohort was observed without their knowledge in a time-series study design. We monitored glove use during venipuncture/IV placement, and face visor use during wound irrigation, pre and postintervention phases. Pre intervention phase the RN's wore gloves 13/51 times (25%), and over a 4 week period post intervention phase they wore gloves 65/70 (93%) ($p<.001$; $RR=3.6$, CI 2.3-5.8). The RN's were observed for another 3 weeks and their continued compliance was 50/56 (89%). The compliance by the RN's 5-7 weeks post intervention phase (89%) was not statistically different compared with 1-4 weeks post intervention phase (93%) ($p=0.5$, $RR=0.9$, CI 0.8-1.1). The MD's pre intervention phase wore gloves 9/51 (18%) vs. 55/59 (93%) over a 4 week period post intervention phase ($p<.001$; $RR=5.3$, CI 2.9-9.6). The entire cohort's success rate on the first attempt at vascular access while wearing gloves was 141/192 (73%) vs. 63/95 (66%) without gloves ($p=0.27$; $RR=1.1$, CI 0.9-1.3). The MD's wore a face visor 0/21 times pre intervention phase vs. 5/14 post intervention phase ($p<.001$). We conclude: (1) intensive educational intervention dramatically improves compliance with universal precautions by RN's and MD's in the ED; (2) this improvement did not extinguish among RN's over a 7 week period post intervention; (3) glove use did not interfere with the proficient performance of vascular access procedures; (4) longer term follow-up data is being collected to better plan for continuing education.

Historical Correlates to Anogenital Trauma in 1,150 Suspected Child Sexual Abuse Victims

D. L. Kerns and M. L. Ritter

Department of Pediatrics,
Santa Clara Valley Medical Center, San Jose, Calif

Between July 1985 and January 1990 comprehensive medical evaluations were performed on 1,150 children and adolescents who were suspected to be victims of sexual abuse. These evaluations included the collection of demographic, historical and behavioral data, and physical examinations including colposcopic photography. A computerized data base was developed for the detailed analysis of these cases. By virtue of anogenital physical findings, the cases were diagnostically classified into five categories: (1) Benign (57.22%), (2) Benign with Reservations (11.39%), (3) Uncertain (4.7%), (4) Suggestive of Trauma (10.09%), and (5) Trauma (16.35%). For purposes of analysis, "Uncertain" cases were dropped, categories (1) and (2) were combined as the "Benign Cluster" (68.61%), and categories (4) and (5) were combined as the "Trauma Cluster" (26.17%). Chi-Square analysis was used to determine the association of a variety of historical variables to the physical finding of anogenital trauma (i.e. categorization in the "Trauma Cluster").

Females were nearly twice as likely as males to have trauma (28.82% vs. 15.81%; $p<0.001$). In females, positive associations to trauma included age greater than 3 years ($p<0.001$), separation from biologic parents ($p<0.01$), acute (vs. elective) visits ($p<0.05$), penile contact ($p<0.001$), penetration ($p<0.001$), pain ($p<0.001$), bleeding ($p<0.001$), ejaculation ($p<0.01$), urinary tract infection ($p<0.01$), and aggression ($p<0.05$). In males, positive associations to trauma included penile contact ($p<0.01$), penetration ($p<0.01$), and feeding disorder ($p<0.05$). Among historical variables not positively associated with trauma were ethnicity, confessions, number of perpetrators, number of episodes, depression/suicide, regression, sexualization, school disturbance and sleep disorder.

Screening for Cocaine Intoxication In Children With Unexplained Seizures in the Emergency Department

S. E. Krug, R. D. Marble, D. L. Lubitz, and T. J. Long

Department of Pediatrics,
Case Western Reserve University School of Medicine,
Cleveland, Ohio

Recent literature has demonstrated a significant incidence of cocaine exposure and intoxication in pediatric populations and suggests an increased susceptibility for cocaine induced convulsions in children. Children presenting for emergency care with an unexplained convulsion may, therefore, represent a population at risk for cocaine intoxication.

All children between the ages of 0 and 16 years presenting to an urban university hospital emergency department (ED) with a history of a convulsion within the preceding 12 hours were considered for study enrollment. Children with a known history of epilepsy or prior seizures, an identifiable traumatic, metabolic or infectious precipitant, or a presentation consistent with a simple febrile seizure were excluded.

As part of their ED evaluation, all enrolled children had blood and urine samples collected for toxicology screening. The presence of the cocaine metabolite benzoylecgonine, was determined via the EMIT® urine assay. All ED visits for the period of the study were reviewed to determine completeness of patient enrollment.

Over a period of one year, 66 children were enrolled, representing 80% of all potential enrollees. 30 of these enrolled patients were then excluded based upon subsequent identification of a cause of their seizure including trauma (5), metabolic (6), infection (7), epilepsy (4) and simple febrile convulsion (8). None of these children had a positive toxicology screen. Of the remaining 36 patients, 4 (11%) had a positive urine toxicology screen for cocaine. Subsequent history confirmed either an intentional (ages 14 & 15 years) or accidental ingestion (ages 14 and 32 months) in all 4 children.

The data from the study suggests that children presenting to an urban ED with an unexplained convulsion represent a group at risk for cocaine intoxication and warrant consideration for toxicology screening.

The Value of Chest Radiographs in the Evaluation of Febrile Infants Less Than Two Years Old

J. A. Taylor, S. Roncevich, E. Kouri, C. Talarico, and R. Schneider

Departments of Pediatrics, Radiology,
and Emergency Medicine,
Carolinas Medical Center, Charlotte, NC

In the evaluation of febrile infants less than 2 years old chest radiographs (CXR) are frequently obtained even in the presence of a normal chest examination. We postulated that if every component of a systematic lung exam in a febrile infant were normal the yield of a CXR would be low. Between December, 1989, and July, 1990, examining physicians in the Emergency Department of a large urban teaching hospital completed a study questionnaire on febrile infants < 2 in whom a CXR was obtained. The presence or absence of the following respiratory signs was recorded: rales, grunting, retractions, nasal flaring, and asymmetry of breath sounds. The child's temperature, age, and resting respiratory rate were also recorded. Tachypnea was defined as a respiratory rate of > 50 in infants 0-6 months old, > 45 for infants 7-12 months old, and > 40 in those 13-24 months old. If all signs were absent the exam was considered negative; if one or more signs were present the exam was positive. CXR were independently classified as pneumonia, no pneumonia or indeterminate by 2 radiologists unaware of the child's clinical condition. Agreement between radiologists was 74% (Kappa = .53). For the analysis CXR were considered positive only if classified as pneumonia by both radiologists.

One hundred thirty-one infants were enrolled: radiologic evidence of pneumonia was found in 32 (24.4%), and no evidence of pneumonia was found in 89 (67.9%); in 10 children (7.6%) the CXR was classified as indeterminate. Although patients with radiographic evidence of pneumonia were more likely to demonstrate positive physical findings than those with negative CXR (20/32 vs. 35/89, P = .04), more than a third of our infants (12/32) with positive radiographs had no findings suggestive of lower respiratory tract infection. Thus our bias was not supported by the findings of this study. An appreciable number of febrile infants 0-2 years old with pneumonia have a normal physical examination of the lungs.

A New Instrument to Improve the Ability of Non-Experts to Identify Infants at Risk of Subsequent Child Abuse or Neglect

D. H. K. Ihnat, J. M. Leventhal, D. V. Cicchetti, D. R. Wasserman, and J. P. Hamilton

Department of Pediatrics,
Yale University School of Medicine, New Haven, Conn,
and Yale–New Haven Hospital

Prior studies have indicated that clinicians can identify some newborns who are at high risk of subsequent child abuse or neglect. To provide a standardized approach to the assessment of risk during the post-partum period, we developed a clinical rating scale and compared the assessments of clinicians who use this scale with those of child abuse experts.

The clinical rating scale (CRS) consisted of 22 risk factors, including items about the mother (e.g. use of drugs), father, past care of children, family, pregnancy, and the mother's in-hospital behaviors. Each item was scored on a 4-point ordinal scale, in which 1 represented no risk, 2 low, 3 moderate, and 4 high risk. For each item, a clear example was given for each level of risk. The score was the sum of those items rated ≥ 2; a total score of ≥ 9 was labeled High Risk.

Pairs of experts in the field of child abuse rated the risk statuses of 32 newborns born to inner city mothers. After jointly interviewing a mother on the postpartum ward, each expert used unstructured clinical judgment to provide an overall assessment of the newborn's risk status, as either high or low risk. The nurses and pediatric residents caring for these same families served as non-expert clinicians and independently assigned risk using the CRS.

The experts' overall assessment, which had an agreement (P_o) of 91% and a kappa of 0.80, served as the gold standard of prediction. Of the 32 assessments, 44% were considered high risk by these experts. Compared to the assessments of the experts, the nurses' CRS's had a sensitivity of 64% and a specificity of 78%, and the pediatricians' CRS's had a sensitivity of 63% and a specificity of 92%.

We conclude that experts agree with each other in their overall evaluations and that using the CRS, non-experts have fair sensitivity and good specificity. The CRS should help clinicians caring for newborns assess the risk of subsequent abuse or neglect and thus focus scarce resources on those at highest risk.

Maltreatment of Children Born to Cocaine Dependent Mothers

D. R. Wasserman and J. M. Leventhal

Department of Pediatrics,
Yale University School of Medicine, New Haven, Conn

Much of the recent rise in national reporting of child abuse and neglect has been attributed to parental substance abuse, particularly the use of cocaine, yet there are no systematic studies that examined this association. The purpose of this ongoing y is to investigate the relationship between maternal cocaine ndency and child maltreatment in a cohort of young chil-

e have identified 43 infants, born between 10/88 and 7/89, se mothers were identified as regular users of cocaine during nancy based on history and the results of urine toxicology ens. These "exposed" infants were matched to a comparison ip of 43 "unexposed" infants whose mothers did not use co- e during pregnancy. Matching was on the basis of birthdate, , method of payment for the hospitalization, and marital sta- of the mother. Through a review of medical records, we de- ined the occurrence of maltreatment (physical abuse, sexual se, or neglect), as well as placements in foster care or with bstitute caretaker. To identify episodes of maltreatment, a ewer who was unaware of the group status categorized each ry as due to abuse, neglect, household violence, or an ac- nt.

uring the first 18 months of life, maltreatment occurred in of the "exposed" vs. 2% of the "unexposed" groups =9.6, 95% C.I.: 1.2-78.6). Physical abuse occurred in 9% of "exposed" vs. 2% of the "unexposed" groups (RR=4.7, 95% : 0.4-35.6), while neglect occurred in 12% vs 0% (P <.05). nges in placement occurred in 23% of the "exposed" vs. 2% he "unexposed" groups (RR=9.6, 95% C.I.: 1.2-78.6). Of the placements, only 2 were directly linked to an episode of mal- tment: 3 occurred while their mothers were in residential g treatment programs and 3 after the mother deserted the dren to the care of a relative.

hildren identified during the neonatal period as regularly "ex- ed" to cocaine *in utero* are at a substantially increased risk both naltreatment and of changes in the primary caretaker during first 18 months of life. Further studies are necessary to de- nine whether intensive interventions can prevent these enting failures.

e Interdisciplinary Evaluations Alleged Sexual Abuse Cases Necessary?

K. Jaudes and M. Martone

Rabida Children's Hospital, Chicago, Ill,
d Department of Pediatrics,
iversity of Chicago Pritzker School of Medicine

Alleged sexually abused children often go through grueling errogations to relate to adults their experiences and even then, ost are not viewed as reliable sources of information. The Vic- n Sensitive Interview Program (VSIP) was initiated to decrease e number of interviews for which a child who allegedly had en sexually abused had to endure. The program brought to- ther the disciplines involved in the evaluation of these cases: spital based medical social worker and pediatrician, state child otective agency worker, police youth officer, and assistant ate's attorney. This team established a protocol for an inves- gative interview to be conducted by a team member.

We compared by t-test analysis preVSIP sexual abuse evalu- ions from 1985 to 1986 (38) with VSIP evaluations (224) from 87 to 1988. There was no significant difference between the two oups in relation to gender or age of victim, physical symptoms, xually transmitted diseases present, age of perpetrator, or ngth of stay in hospital. There were significant differences be- veen the two groups in (1) number of interviews ($p<0.003$), 11% reVSIP versus 80% VSIP receiving only one interview, (2) in- icated cases of sexual abuse ($p<0.006$), 68% preVSIP versus 85% SIP, (3) identification of the perpetrator ($p<0.026$), 70% preVSIP ersus 85% VSIP, and (4) charges pressed ($p<0.029$), 32% pre- SIP versus 55% VSIP.

To assess if police evaluations of child sexual abuse cases were imilar, we compared VSIP cases (224) to cases (235) for the same ears in a designated police area that did not have an interdis- iplinary program. Significant differences were found for iden- fication of the perpetrator ($p<0.000$), 85% VSIP versus 37% Po- ce and charges pressed ($p<0.018$), 55% VSIP versus 40% Police. here were no difference in gender of the victim but the children interviewed by the police were slightly younger (6.7 years compared to 7.3 years of those in VSIP).

From this study, interdisciplinary evaluations of alleged sexually abused children not only decreased the number of interviews a child must undergo but also increased the likelihood of indicated cases, identification of the perpetrator, and charges being pressed. We strongly recommend formation of interdisciplinary teams to assess allegedly sexually abused children.

GENERAL PEDIATRICS

Doctorhoppers: Myth or Reality?

C. Gosselink, D. Brazdziunas, E. Ekwo, A. Kresheck, and M. Lehmann

Department of Pediatrics, University of Chicago (Ill)/
La Rabida Children's Hospital and Research Center

ER pediatricians frequently claim that one of the reasons for congested emergency services is that caregivers (CGs), unconvinced that their children's symptoms are being correctly diagnosed or treated, go from doctor to doctor for the same presenting complaint. "Doctorhoppers" (DHs), as these CGs are commonly called, are perceived as unnecessarily overburdening ER services when they should return to their child's primary care provider to seek reassurance or better understanding about their child's condition. To examine whether DHs really do exist, a sample of CGs of children visiting an inner-city ER during a 2-month period were surveyed by trained interviewers regarding sociodemographics, health care use, and medical history. CGs were asked how many times in the past 2 weeks they had taken their child to another doctor, clinic, or ER for the same presenting complaints.

116 (16.5%) of the 704 CGs acknowledged having taken their child to another doctor in the last 2 weeks for the same presenting complaints. 72.4% had only gone to one other doctor, although 32 (27.6%) had seen ≥2 for the same symptoms. 47 (40.5%) of the CGs had received written instructions from the other doctor and all claimed they were able to understand this information. However, reasons given for not returning to the other doctor included wanting a 2nd opinion (28.7%), the doctor's office being closed (20.9%), and not trusting the other doctor (13.9%).

Multiple logistic regression was performed to compare DHs with the other 588 sampled CGs (NonDHs) and odds ratios (OR) were calculated. DHs were significantly more likely than NonDHs to be single (OR=3.1), to have been aware of their child's symptoms for more than 24 hours (OR=2.7), to state they would go to another doctor if their child did not seem to be getting better (OR=1.9), and required >15 minutes to get to the ER (OR=1.8). However, they were significantly less likely than nonDHs to mention convenience of ER location (OR=.30), be up to date on their child's shots (OR=.37), or to be familiar with the study ER (OR=.62).

We conclude that DHs do indeed exist. However, we believe DHs are comprised of highly-motivated CGs who appear to be concerned about their children's welfare. We suggest that better CG-doctor relations and education could encourage CGs to return to the child's primary care physician and may improve immunization status. This would be better for the child and could help reduce ER overcrowding.

What Factors Predict School Absence in Children With Chronic Medical Conditions?: A Controlled Population Based Study

F. C. Jarman and M. C. Starr

Department of Pediatrics,
University of Massachusetts Medical Centre, Worcester

Excessive school absence has been identified as the single most important administrative problem facing educators in the United States. School absence may be associated with poor achievement, psychosocial problems, and early school drop-out. Children with chronic medical conditions are known to be at high risk for school absence, although the specific determinants and correlates of absence in a community-representative sample of chronically ill and well children remain to be further clarified.

We prospectively surveyed parents of all 1601 fourth grade students attending the 41 public elementary schools in Worcester using a standardized health screening instrument. Of the 1168 (73%) children who participated in the study, 306 (26%) had chronic medical conditions, and these children were individually paired with healthy classroom controls matched for age, sex, race, and sociodemographic characteristics. Cases and controls were then compared on standardized measures of behavior, academic performance, perceived self competence, health locus of control, and number of days absent over the preceding school year. The predictors of school absence were also examined.

Children with chronic medical conditions were absent an average of 10.0 days over the preceding school year, compared to 8.2 days for healthy controls (p<.006). In both groups, univariate analysis revealed school absence to be significantly associated with non-white race (p<.001), lower socioeconomic status (p<.001), and parent perceptions of their children being less well (p<.001). In chronically ill children but not healthy controls school absence was significantly correlated with female sex (p<.001), greater physical limitations (p<.001), and lower academic aptitude (p<.01) and achievement (p<.001). School absence was not related to the child's diagnosis, whether or not the child received special education services, parent or teacher rated child behavior problems, child health locus of control, or child self-perceptions (p>.05). Multiple regression analysis identified family socioeconomic status and degree of physical limitation as the only independent predictors of school absence in chronically ill children; these variables explained 16% of the total variance. For healthy controls, parent perception of child health status was the only independent predictor of school absence identified, accounting for 10% of the total variance.

We conclude that school absence has different correlates in chronically ill compared to healthy children, despite only a 2 day per year attendance discrepancy between the two groups. Children with chronic medical conditions appear to be more vulnerable to the effects of time off school than their healthy peers.

Comparison of Two Methods of Assessing Appropriateness of Admission

R. Kowaleski, P. Griffin, and M. Li

Department of Paediatrics,
Children's Hospital of Eastern Ontario, Ottawa

Interest in limiting unnecessary expenditures in inpatient hosital care has stimulated the development of a number of methds for assessing appropriateness of hospital admission. We ompared two, the Intensity-Service-Discharge-Appropriateess (ISDA) criteria and the Pediatric Appropriateness Evaluaon Protocol (PAEP). Each consists of explicit, objective, iagnosis-independent criteria that are designed to require minimal subjective judgment. However, they differ in many respects in their composition and application.

All non-psychiatric admissions to CHEO every 12th day in 1989 ere retrospectively reviewed. Three raters reviewed each record: the first used PAEP, the second ISDA; their results were used in the comparison of the two methods. The third rater alrnated the two to determine interrater reliability with each. 778 of a possible 786 records were assessed. Overall rate of appropriate admission (RIA) was similar: PAEP=21.3%, DA=21.0%. However, general agreement (GA) was only .5%, kappa(k)=0.33, and there were significant differences hen admissions were examined by source:

	PAEP(RIA)	ISDA(RIA)	
Emergent (E)	7.1%	20.6%	p<.001
Elective (L)*	81.7%	17.5%	p<.001
Urgent (U)	32.8%	53.6%	p<.01
Neonatal (N)	3.6%	0.0%	N.S.

*excludes short stay surgery

A few major differences in PAEP and ISDA accounted for these discrepancies. PAEP requires elective procedures be done on the day of admission; ISDA does not. E and U admissions must meet two different ISDA criteria (severity of illness, intensity of service), but only one PAEP criterion.

Interrater reliability with PAEP showed GA of 93.4%, k=0.82; with ISDA, GA=89.0%, k=0.71; the difference in the two kappas was significant at p<.05. Considering only E and U admissions, the two kappas were similar: PAEP, k=0.70; ISDA, k=0.67.

PAEP, being brief, was easily committed to memory and could be applied more quickly than ISDA, which consists of many pages of criteria. Nevertheless, the two showed similar interrater reliability in assessing E and U admissions. Although overall RIA is similar with each, PAEP and ISDA exhibited frequent disagreement in individual patients.

Validity, Bias, and 'Overcall' in Interpreting Chest Radiographs in Young Febrile Children

M. S. Kramer, R. Roberts-Brauer, and R. Williams

Departments of Pediatrics
and of Epidemiology
and Biostatistics,
McGill University, Montreal, Quebec

Few studies have examined the diagnostic validity of the examining physician's interpretation of chest radiographs in young febrile children, and none (to our knowledge) the extent to which the "official" (i.e., the radiologist's) reading may be biased by access to the examining physician's reading and to other clinical information. We studied 229 consecutive chest radiographs obtained in febrile, nonasthmatic children 3 to 24 months of age who presented to a children's hospital emergency department between March 1989 and August 1990. We compared the readings by the examining staff pediatrician, the subsequent (usually next day) official pediatric radiologist's reading, and a "blind" reading by a pediatric radiologist. The official radiologist had access to the examining pediatrician's readings and the clinical information provided on the x-ray requisition. The blind radiologist knew only that each child was 3 to 24 months of age and febrile; he was asked to judge the presence or absence of pneumonia.

Of the 229 total radiographs, the examining pediatrician interpreted 53 (23%) as demonstrating pneumonia, a significantly (P<.01 by McNemar χ-test) lower number (72, or 31%) than the official radiologist but similar to that of the blind radiologist (47, or 21%). The positive predictive value (PPV) of the examining pediatrician's reading was significantly (P<.001) lower when based on the blind radiologist as gold standard (.34) than when based on the official radiologist (.70). When the analysis was restricted to children without suggestive clinical signs of pneumonia, PPV decreased when based on the blind reading (.19) but not when based on the official reading (.80). Agreement between the official and blind radiologists' readings was barely better than could be explained by chance [(κ=.15 (95% confidence interval=.05-.25)].

These results indicate that official interpretations systematically "overcall" pneumonia, particularly in cases without suggestive clinical findings, and appear to be influenced (biased) by the examining physician's reading. Since these tendencies can lead to unnecessary antibiotic treatment and hospital admission, strategies to reduce them should receive high priority.

An Analysis of Mental Health Service Utilization by Children in Foster Care in California

N. Halfon, G. Berkowitz, and L. Klee

Center for the Vulnerable Child,
Children's Hospital, Oakland, Calif

An examination of Medi-Cal paid claims was undertaken to assess the utilization of mental health services by children in California's foster care system. Using unduplicated counts of service use and diagnoses, it was determined that children in foster care

ount for 41% of all users of mental health services even though
y represent less than 4% of Medi-Cal eligibles. When parti-
ied into specific service categories, children in foster care ac-
nt for 53% of all psychologist visits, 47% of psychiatry visits,
% of Short Doyle/Medi-Cal inpatient hospitalization in public
spitals, and 27% of inpatient psychiatric hospitalizations. Ex-
nditure for services paralleled utilization frequency. When
mpared to the non-foster care Medi-Cal eligible child popu-
on, children in foster care have 10 - 20 times the rate of uti-
ation per eligible for selected services. For children in foster
e 75% of all diagnoses for billed services were accounted for
four diagnoses: adjustment disorders (28.6%); conduct dis-
ders (20.5%); anxiety disorders (13.8%); and emotional disor-
s (11.9%), with clear age related differences in the distribution
diagnoses. This study raised several questions about the nat-
l histories of mental health disorders of children in foster care,
availability of appropriate services as well as questions about
need for early intervention and preventive mental health ser-
es.

e Relation of Family Mobility Children's Emotional d School Functioning

A. Simpson and M. G. Fowler

ational Center for Health Statistics,
yattsville, Md

The impact of multiple family moves on childrens' emotional
d school adaptation have not been well delineated. To address
is issue, we utilized data from the 1988 National Health In-
rview Survey on Child Health (NHIS-CH), a cross-sectional
rvey which included a representative national sample of 10,362
hool aged children in grades 1 through 12.

We found that 39 percent of children aged 6 to 17 had moved
ree or more times in their lifetime—42 percent of Hispanic chil-
ren, 39 percent of whites, and 34 percent of black children.
mong children living below the poverty level, 48 percent had
oved multiple times versus 37 percent of children at or above
e poverty level. Likewise, 53 percent of children on Medicaid
ad moved three or more times compared to only 36 percent of
ildren with private health insurance. In addition, 51 percent
f children in one parent families moved three or more times,
hile only 35 percent of children in two parent families moved
at often. Using multiple logistic regression to control for de-
ographic variables, children who moved three or more times
vere 2.4 times as likely to have had emotional problems, 2.2 times
s likely to have received psychological help, 1.7 times as likely
o have repeated a grade, and to have been suspended or expelled
rom school compared to children who had never moved. Like-
vise, using multiple linear regression, the adjusted mean score
n the Behavior Problem Index for children who had moved three
r more times was significantly higher than for children who had
ever moved, 6.8 versus 5.5. These findings confirm that children
vho move multiple times are at high risk for emotional and school
roblems.

Biofeedback: Initial Success in Treating Recurrent Abdominal Pain

A. J. Rosenberg and T. Whitehead

Department of Pediatrics,
University of Kansas Medical Center, Kansas City

Recurrent abdominal pain (RAP) is reported in 16% of school age children. A study using progressive relaxation with biofeedback in children with RAP was initiated at the University of Kansas Medical Center. RAP is defined as a minimum of three occurrences of significant abdominal pain within at least a three month period interfering with normal activity. Sixteen children, 13 girls and 3 boys with an average age of 10 years (6-14 years) met the criteria for RAP. The frequency of abdominal pain averaged 13 episodes per week per child. RAP children were randomized into two groups. The Treatment Group (Group I) consisted of 8 girls, average age 10 years with an average of 15 episodes of pain per week, and the Control Group (Group II) 8 children, 3 boys and 5 girls, average age 11 years, averaging 11 episodes of pain per week. All children were evaluated for frequency and severity of pain by self report at entry and after the six week period. The biofeedback treatment group was taught progressive relaxation while being continuously monitored for skin temperature and EMG, which were converted to digital pulse and displayed to the subject as light and sound on a BMI SRI PRO series model 421 biofeedback instrument. Subjects attended six weekly relaxation - biofeedback sessions. Subjects were given a relaxation tape with which to practice at home between sessions. After six weeks, Group I children had a reduction of abdominal pain to an average of less than one episode per week. This was statistically significant in the relief of abdominal pain in the treatment group at alpha level .05, using the t test of paired samples. Five of the biofeedback children (63%) reported complete absence of abdominal pain. Although the frequency of abdominal pain in the Group II fell to an average of five episodes of pain per week, this was not statistically significant. This demonstrates the Hawthorn effect in the control group of symptom reduction as a result of participating in a study. Biofeedback training had a significant effect on reduction of abdominal pain over the six weeks of training sessions. This treatment method may have a significant impact on reducing recurrent abdominal pain in children and its sequelae in adults.

Are School-Based Clinics Serving the High-Risk Student?

J. W. Stout and C. R. Anderman

Departments of Pediatrics and Epidemiology,
University of Washington, Seattle

Oregon's school-based clinics offer comprehensive primary care, including services designed to alter risk-taking behavior. However, it is not clear whether the students who utilize these services are in fact those at increased risk. The purpose of this study is to examine whether these clinics are reaching the population engaging in various kinds of risk-taking behavior, such as substance use and unprotected sex. Data concerning clinic utilization and risk-taking behavior were collected with an 88-item adolescent health survey, administered in the fall of 1990 to students in four Oregon high schools where school-based clinics have been operating for at least three years. In addition to treatment of acute illness and injury, these clinics provide counseling and care for reproductive health which may include prescribing (but not dispensing) contraceptives, and counseling or referral for substance use and mental health problems. Of the 2530 students who completed the survey, 50% reported ever using the clinic. In the area of substance use, students using clinic services were significantly more likely to engage in binge drinking (27% vs. 15%, p<.01), regular cigarette smoking (19% vs. 11%, p<.01), or marijuana smoking (28% vs. 16%, p<.01) than those who do not use clinic services. Regarding reproductive health, clinic utilizers were significantly more likely to be currently sexually active than non-utilizers (35% vs. 19%, p<.01). In the area of mental health, students who use the clinic were significantly more likely to be suicidal than non-utilizers (20% vs. 13%, p<.01). In conclusion, students who utilize clinic services are more likely to engage in risk-taking behavior than those who do not utilize these services. Subsequent analyses will determine whether risk-taking behaviors are addressed during clinic visits, and further characterize all students engaging in these risk-taking behaviors.

A Clinic-Based Intervention to Promote Literacy

R. D. Needlman, L. E. Fried, and B. S. Zuckerman

Division of Developmental and Behavioral Pediatrics,
Boston (Mass) City Hospital

Educational research has shown that exposure to story books is an especially potent stimulus to preschool language development and the acquisition of literacy. To encourage book use among children at risk, we developed and evaluated a primary care clinic-based program which included (1) volunteers who read aloud to children in the waiting room, modeling book use for parents; (2) individualized guidance on book use by pediatricians; and (3) distribution of developmentally and culturally appropriate books to children age 6 months through 5 years at each clinic visit. To assess program effectiveness, 79 parents were interviewed in the waiting room several months after the program began. Thirty-nine percent of the parents received AFDC, 40% were single, 49% were Black, and 3% were White. In order to minimize misreporting, parents were asked to provide a 24-hour recall of everything they did with their child, modelled after a 24-hour diet recall, and to state their child's three favorite activities. After controlling for possible confounders, parents who had received one or more books were four times more likely to report looking at books with their children in the last 24 hours, or that looking at books was a favorite activity (adjusted odds ratio = 4.05, P = .028). This association was strongest among parents receiving AFDC (odds ratio = 7.8, P = .001). This preliminary study suggests that pediatricians can play a role in enriching children's early literacy environments, especially for children at high risk for school failure.

A Critical Appraisal of the Quality of Pediatric Journal Articles That Evaluate Diagnostic Tests

A. Bates, P. X. Margolis, and A. E. Evans

Departments of Pediatrics and Medicine,
University of North Carolina, Chapel Hill, and
Indiana University, Indianapolis

Studies reported in peer-reviewed journals play a major role in disseminating information about the value of diagnostic tests and therefore may affect the quality of patient care. We conducted a systematic critical appraisal of the quality of pediatric journal articles that evaluate diagnostic tests.

We identified all studies of diagnostic tests published in three major pediatric journals over a three year period. Articles were included if they evaluated a test for clinical use in diagnosis, presented original data, and used human subjects. We used 28 criteria to evaluate the following 5 areas of study quality: adequacy of the patient sample, application of diagnostic test, application of gold standard, reporting of results, and discussion of potential utility.

Forty-two articles met our inclusion criteria. Half had serious methodologic short-comings. Of these serious problems, 80% were a result of uneven application of the gold standard; either eligible patients were excluded from analysis because the gold standard had not been applied, or patients with positive diagnostic test results were more likely to have had a definitive work-up compared to those who tested negative. The remaining 20% used a study sample with unusually prevalent or severe disease. An average of 10 of the remaining 26 criteria were not satisfied (range 3 to 20). Most involved failing to report information: the precision of test characteristics, (94%), uninterpretable test results, (86%), technical or observer variability, (83%), and the accuracy of the gold standard, (75%).

A striking number of the pediatric journal articles evaluating diagnostic tests may be so seriously flawed that their results are of questionable validity. These findings suggest that information about methodologic standards for conducting, evaluating, and reporting studies of diagnostic tests should be more widely disseminated. Journal editors and reviewers might also benefit from more structured approaches to assessing studies of diagnostic tests.

Educational Effectiveness of a Lead Poisoning Video

S. Melman, M. Schorr, R. Lempert, M. Polansky

Department of Pediatrics,
Hahnemann University Hospital, Philadelphia, Pa

Lead poisoning is a serious pediatric health threat, which often causes impaired learning and behavioral disturbances. In Philadelphia, over 30% of children <5 years of age are estimated to have lead levels >0.70 μmol/L, yet only 13% of high-risk children were screened in 1989. We developed a ten-minute educational video to teach parents lead poisoning prevention and the importance of screening. The video includes scenes of children playing among peeling paint and dust, inspectors checking homes for lead paint content, and a child being screened for lead poisoning. The purpose of this study was to test the educational effectiveness of this video.

50 English-speaking parents from our inner-city pediatric clinic were randomly assigned to view either the lead video or a commercially available general safety video. Both groups took pre and post-tests to measure their lead poisoning knowledge.

The lead and control groups were comparable in terms of age (31.3 ± 7.0 S.D. vs. 31.5 ± 8.6), gender (proportion of females 0.63 ± 0.48 vs. 0.83 ± 0.38), highest grade level attained (11.8 ± 0.9 vs. 11.8 ± 1.8), insurance (proportion of private 0.42 ± 0.49 vs. 0.26 ± 0.44), and baseline score (9.6 ± 0.4 vs. 10.6 ± 0.4).

The mean increase in score for the lead-video group was 33.0% (SE = 6.3%) in comparison to an 1.5% decrease (SE = 3.0%) for the control group (p < .001). Even after controlling for baseline score, age, sex, educational level, and insurance coverage, a multiple regression confirmed a strongly significant improvement in the lead video group.

The results indicate that this brief educational intervention was effective in significantly increasing short-term lead poisoning knowledge in an inner-city clinic parent population. A six-month follow-up study is planned to test retention. By successfully educating parents about the seriousness of lead poisoning, we will encourage their efforts towards prevention and early detection.

Impact of Shorter Working Hours on Pediatric Housestaff Training

A. Willenborg, S. Shelov, and D. Neuspiel

Department of Pediatrics,
Albert Einstein College of Medicine, Bronx, NY

Residency training has traditionally involved extended hours and long work weeks. In July 1989 New York State implemented strict limitations on resident working hours. In order to monitor the effects of these changes on patient care, resident education, and the personal lives of pediatric housestaff, we initiated a longitudinal study in the spring 1989. Pediatric residents from 30 New York State(NY), and 14 Chicago and Los Angeles where no such changes were instituted (CHI/LA) programs were asked to complete a questionnaire both prior to the onset of limitations (Spring 1989) and one year later, including information concerning demographic data, patient care, education, supervision, and personal issues. In 1989, 533 residents from 22 NY and 10 CHI/LA programs completed questionnaires: in 1980, 439 residents from 16 NY and 8 CHI/LA programs participated. Mean maximum consecutive work hours were reported as:

	1989			1990		
	NY	CHI/LA	P	NY	CHI/LA	P
Inpatient (S.D.)	34(6)	35(3)	.05	30(5)	36(4)	<.0005
Outpatient (S.D.)	17(10)	20(10)	.03	15(8)	20(10)	<.0005

NY residents reported more sleep while on inpatient rotations, greater time with their spouse or significant other, and increased time for social life and personal needs compared with CHI/LA residents in 1990 (all p<.005), but no in 1989 (all NS). However, NY residents spent more time than CHI/LA residents performing non-physician tasks and participating in sign-out rounds in both years (p<.005).

It appears that the limitation of work hours has improved the quality of life for NY pediatric residents. However, NY residents continue to spend more time doing non-physician tasks and in sign-out rounds. The effects of shorter working hours on education, patient care, and supervision were also examined any analyses of these differences also will be presented.

PREVENTION AND EPIDEMIOLOGY

munization Opportunities Missed nong Urban Poor Children

M. McConnochie and K. J. Roghmann

partment of Pediatrics,
chester (NY) General Hospital, University of Rochester

Low immunization (IZ) rates among United States preschool-e children suggest a need for altered vaccination practices. mputer IZ and encounter records as well as traditional medical ords were reviewed to ascertain IZ rates and missed oppor-ities (MOs) for vaccine administration among 540 children. bjects included all preschool children over 30 months of age o were active for at least 6 months in an urban, hospital-based imary care practice serving lower SES families (74% Medicaid-vered visits). Subjects averaged 17 visits over their first three ars. Despite such frequent contacts, the point prevalence at straction (mean age 4.4 yrs) for lack of one or more recom-ended IZs was 29%; 8% lacked MMR, 20% lacked Hib, 9% cked two or more DPT, and 5% lacked two or more OPV. Many ore (79%) experienced at least one period of undervaccination any time during their first 36 months.

Any visit when IZs were due but not given was counted as MO; multiple IZs were due, multiple MOs were counted. For the % of children with a period of undervaccination, there were average of 7.3 missed opportunities per child. Although over lf of MOs occurred during an acute illness, 28%, 11% and 4% curred at well child visits, follow-up visits and chronic illness sits, respectively. Eighteen percent of MOs occurred at Emer-ency Department visits where IZ records were not readily avail-le. Had opportunities not been missed, the average undervac-nation period would have been reduced by 4.8, 4.7, 4.4 and 5.3 onths for DPT, OPV, MMR and Hib.

Thoughtful evaluation of IZ contraindications at acute visits, adily available IZ records, and better use of IZ opportunities t non-acute visits would reduce undervaccination risks substan-ally.

redictors of Parental Injury Prevention Behavior

. F. Schwarz, C. B. Forrest, J. A. Grisso,
. G. Miles, and V. M. Wolfson

epartment of Pediatrics
nd Clinical Epidemiology Unit, University of Pennsylvania
chool of Medicine, Philadelphia

Effective injury prevention strategies need to target those who re least likely to change their behavior. We evaluated parental njury prevention behavior that occurred as a result of a fall in hildren under 2 years. Using structured interviews, we assessed amilies of 123 consecutive children evaluated in 11 emergency ooms involved in an ongoing injury surveillance program. We heorized that pre-fall injury prevention behavior, circumstances f the fall, and demographics of the child and family could be sed to describe families as those who made changes (CH) and thers who did not change (NCH) their injury prevention be-avior.

We found significant differences in injury circumstances between CH and NCH groups. For example, CH infants were more likely to have sustained falls from heights >36 inches ($p<.01$) and in settings where home modifications could occur (indoors v. outdoors, $p<.01$, and on indoor v. outdoor stairwells, $p.<001$). Of falls from beds, 89% were associated with CHs ($p<.05$). CHs were more common in children learning to walk than in those already walking ($p<.05$); and in keeping with this finding, anterior head injuries were more common in CHs than posterior head trauma ($p<.05$). Fallers 18-24 months were more likely NCHs ($p<.01$). Of falls involving girls 78% were CHs ($p<.10$). Maternal perception of the injury as severe ($p<.05$) and high levels of stress ($p<.05$) were associated with CHs; surprisingly, pre-fall injury prevention behavior, household composition, caregiver age, socioeconomic status and social support had no effect on injury prevention behavior.

We conclude that specific patient characteristics and circumstances of the fall can be identified as important predictors of injury prevention behavior. Strategies to prevent injuries due to falls should focus on these factors in order to target groups in need of additional intervention.

The Functional Impact of Asthma

J. M Perrin, M. L. Weitzman, and S. L. Gortmaker

Children's Service, Massachusetts General Hospital,
and Harvard School of Public Health, Boston;
University of Rochester (NY) School of Medicine

Asthma and other chronic health conditions affect the functioning of children, as measured by days spent in bed or hospital and by school absence. We used the 1988 Child Health Supplement (CHS) to the National Health Interview Survey to examine the extent of asthma-related functional disability in this nationally representative random household survey. The 1988 CHS provides data about health status, utilization, functional impact, and psychological status for 17,110 children. All analyses were performed by linear regression, controlling for age and maternal education.

Children with asthma spent more than twice as many days in bed for illness (7.56 vs 3.01, $p<0.001$), had four times more hospital days (1.08 vs 0.23; $p<0.0001$), lost more days of school (7.82 vs 3.90; $p<0.0001$), and had higher scores on a behavior problems index ($p<0.01$) than children without asthma. Boys with asthma missed more days of school than did girls ($p<0.05$). Among those with asthma, black children experienced no significant differences in bed or hospital days or school absence, although they were reported by their parents as being in poorer health ($p<0.004$) and had fewer doctor visits (4.63 vs 7.05, $p<0.02$) than did white children with asthma. Lower maternal education was independently associated with increased home and hospital bed days and school absence and decreased reported general health status.

These findings indicate that asthma has a significant effect on children's participation in usual daily activities. Black children with asthma, despite apparently similar functional impact of asthma, appear to use medical services less than do white children with asthma.

Avoidable Pediatric Hospital Use: A Comparison of Admitting Physician Judgment With Utilization Review

J. L. Soulen, A. K. Duggan, and C. DeAngelis

Department of Pediatrics,
Johns Hopkins University, Baltimore, Md

Current mechanisms for identifying avoidable hospital use, such as Utilization Review (UR), rely on the opinion of persons other than those caring for the patient. The agreement between hospital use ruled unjustified by UR and use judged avoidable by admitting physicians is unknown. This study determined 1) the proportion of acute, medical admissions to an urban teaching hospital which the admitting physician considered potentially avoidable; 2) specific services that would have helped prevent avoidable admissions; 3) social factors influencing decisions to admit; and 4) the agreement between physician judgment and UR in identifying avoidable hospital use.

A random sample ($n=600$) of acute medical admissions from March to October, 1990 was chosen. Questionnaires were completed by 96 admitting physicians, with 90% completed within 3 days of admission. Responses were compared with hospital UR data.

Admitting physicians judged 166 of 600 admissions (27.7%) as potentially avoidable had specific services been available and accessible. Services most frequently desired were a 24 hour short stay unit (23.0% of all admissions), an outpatient discharge coordinator to arrange known services (7.5%), and home nursing services (4.8%). UR identified only two (1.2%) of these 166 admissions as medically unjustified. Social context contributed to 88 of 600 admissions (14.7%). The major social factors were not trusting the family (39/88 = 44%), family overwhelmed (41%), and not knowing the family well (18%). Thirty eight (6.3%) of 600 would not have been admitted if not for social factors. UR identified only one (2.6%) of these 38 admissions as medically unjustified. Physicians identified services that might have helped prevent admission for 30 of these 38. Of the 434 admissions which physicians judged unavoidable, UR identified none as medically unjustified.

We conclude that 1) admitting physicians identified a large number of avoidable admissions which were not identified by UR, and 2) Utilization Review did not identify admissions as unjustified when admission was needed. Policy implications will be discussed.

Lead Intoxication in Early Infancy

M. W. Shannon and J. W. Graef

Department of Pediatrics,
Harvard Medical School,
and Department of Medicine,
Children's Hospital, Boston, Mass

The traditional view of childhood plumbism is that it is a disease of ambulatory toddlers who live in dilapidated housing and ingest lead-based paint chips or dust. However, this belief potentially serves both to discourage testing of young infants and, if lead poisoning is discovered, to divert practitioners from obtaining information on all potential lead sources. We reviewed our 4 year experience in the management of infants who developed plumbism in the first year of life in order to characterize this younger age group. This study was undertaken in a Lead/Toxicology referral program within the state of MA, whose comprehensive lead laws include extensive (and, recently, mandatory) screening of all children beginning by age 1 year. Over the 4 years, of 370 new patients enrolled in our clinic, 49 (13%) were $\leqslant 1$ year. Mean age was 10 months (range 1-12 months). Six patients < 9 months were detected through select rather than routine screening. Mean peak whole blood lead level was 1.87 umol/L (range 1.01-3.02 umol/L) while mean peak zinc protoporphyrin was 1.20 umol/L. Twenty-two patients (45%) had a hemoglobin < 114 g/L. No infants had clinical signs of lead intoxication. Only 12 patients (25%) had parents who were welfare dependent. Sixty-three percent were non-ambulatory at the time lead poisoning was diagnosed; 34% had a history of pica. Likely sources of lead poisoning included household renovation ($n=20$), ingestion of lead-based paint ($n=8$), formula preparation with lead-contaminated water ($n=9$), indeterminate ($n=7$) and congenital ($n=1$). The 9 cases of plumbism from formula preparation (7 of which were confirmed by water analysis and review of preparation practices) were unexpected and occurred after either: 1) use of first draw morning water to reconstitute a days supply of formula, 2) boiling tap water before reconstituting formula, thereby increasing its lead concentration or 3) inadvertently boiling water in lead-containing vessels.

From these data we conclude: 1) lead intoxication occurs at significant frequency in young, non-ambulatory infants, 2) pica is a less frequent cause of plumbism in this age group, 3) unsafe formula preparation practices may expose infants to lead throughout the first year of life and 4) lead screening of all infants, regardless of socioeconomic status should begin by age 1 year if not before.

Children's Household Exposure to Guns

Y. D. Senturia, A. M. Teuscher, and K. K. Christoffel

Pediatric Practice Research Group,
Children's Memorial Hospital, Chicago, Ill

OBJECTIVES: To determine what proportion of households with children who go to pediatricians contains firearms, the types owned, purposes for which they are kept, condition in which they are stored, and the social correlates of each.

METHODS: In-office completion of a short questionnaire by parents of all children attending 20 participating pediatric offices during 1 week study period.

RESULTS: 1608 questionnaires completed in the first 11 offices have been analyzed. The % of respondents reporting any gun ownership (GO) varied independently by practice (mean: 29%; range: 6-53%; $P<.00001$) and by area of residence (urban (U): 20%, suburban (S): 31%, rural (R): 57%; $P<.00001$). Homes with males >17 years were more likely to own guns ($P<.0001$. U: $P=.0015$; S: $P=.13$; R: $P=.02$). As the number of children <5 years increased, GO decreased ($P<.06$).

Type of firearm owned varied by area:

	Urban	Suburban	Rural	
Rifle (RIF)	12%	20%	47%	$P<.0001$
Handgun (HG)	9%	11%	23%	$P<.0001$

RIF were usually kept for recreation (72%); HG for self-protection (50%) or recreation (54%). The majority of firearms were stored in the bedroom (52%). HG were more often kept locked (LK) 51% and loaded (LD) 24% than RIF (LK, 38%: $P<.01$; LD, 3%: $P<.0001$). HG were more often reported loaded and not locked than RIF (5.3% vs 1.3%: $P<.01$).

CONCLUSIONS: (1) GO is more common in rural areas and in homes without preschool children. (2) GO is more common in homes with adult males. (3) Anticipatory safety guidance regarding children and guns must be tailored to patterns of actual gun ownership, which vary from area to area and practice to practice.

Finding the Missing Data—a Statewide System for Injury Surveillance in the Pediatric Office Setting

J. K. Sanders, E. R. Waring, and J. R. Zanga

Division of General Pediatrics and Emergency Care,
Children's Medical Center, Richmond, Va

Injury is the leading cause of death among children ages 0-19 in the United States. In 1985, over 20,000 children and adolescents died in the United States due to injuries. Mortality statistics alone do not accurately reflect the extent of the injury problem. Indeed, deaths due to injury are just the tip of the iceberg. Nonfatal injury statistics further illuminate the injury problem. A study in Massachusetts estimated that for every injury related death, there are 45 injuries requiring hospital admission and 1,300 injuries requiring emergency department treatment. Because nonfatal injury statistics are generally derived from hospital discharge data, they still do not fully depict the extent of the problem. It is the investigator's belief that a large number of childhood injuries are being seen and treated in the physician's office setting and are not being captured by routine injury surveillance. Therefore, a childhood injury surveillance system has been developed in Virginia to track the incidence of childhood injuries not requiring admission to the hospital system. The objectives are to collect data that will add to our ability to determine injury trends and to develop injury prevention strategies based on trends revealed by the surveillance data.

Sixty private pediatricians, representing virtually every geographic region in the state, have agreed to record information on a monthly basis, using a specially designed instrument, about children seen and treated in their practices for injuries. Monthly physician return rates average 75%. Categories of data collection include patient age, sex, race, family income, agent of injury, location of injury, cause of injury, pathology and severity.

Eight months of data indicate that 2,232 injured children have been treated in the office. Falls, collision with objects and collision with persons head the list of causes. While most injuries are mild, 34% are moderate to severe. Data analysis highlights the gaps in hospital based injury surveillance.

We conclude that injury surveillance data from pediatricians' offices significantly adds to our knowledge of injury epidemiology.

nagement of Childhood Lead Poisoning: A Survey

Glotzer and H. Bauchner

partment of Pediatrics,
ston (Mass) University School of Medicine,
d Boston City Hospital

ublished recommendations (1985) for the management of ldhood lead (Pb) poisoning suggest the use of EDTA prov- tion testing and chelation as the mainstay of treatment for od Pb (BPb) levels between 25 and 55 μg/dL. Since 1985 ev- nce has accumulated indicating that: 1) levels of BPb 25 μg/dL are detrimental to cognitive development; 2) EDTA vocation testing may result in potentially harmful shifts in the dy Pb burden; and, 3) oral agents such as penicillamine (PCA) d DMSA are effective in reducing elevated Pb levels. To de- mine how this evidence impacts on the management of child- od Pb poisoning we surveyed the Pb poisoning clinics of pe- tric departments in the cities estimated by the U.S. Public alth Service to have the largest number of children affected by poisoning.

21 of 43 (49%) surveys were completed. Respondents indicated at the lowest BPb level for which they would use a chelating ent to reduce the Pb burden was: ≥ 40 μg/dL (24%), 35 μg/dL %), 30 μg/dL (24%) and 25 μg/dL (48%). For the following BPb vels respondents indicated their initial recommended manage- ent of an asymptomatic child with BPb elevation would be:

	25-29 μg/dL	30-34 μg/dL	35-39 μg/dL	40-44 μg/dL	45-49 μg/dL	50-55 μg/dL
No chelation	40%	25%	20%	5%	5%	0%
EDTA if Prov+	40%	45%	55%	50%	40%	20%
EDTA chelation	5%	5%	5%	40%	50%	75%
PCA	10%	20%	15%	5%	5%	5%
DMSA	5%	5%	5%	0%	0%	0%

For a child with a negative EDTA provocation test, with the llowing BPb levels, the percent of respondents recommending e use of any chelation therapy is as follows: 25-29 μg/dL (12%), -34 μg/dL (25%), 35-39 μg/dL (25%), 40-44 μg/dL (31%), 45- μg/dL (50%) and 50-55 μg/dL (62%).

The results of this survey indicate that: (1) The majority of chil- ren with elevated BPb burdens are managed using EDTA. Only small minority of Pb clinics currently use oral chelating agents;) The EDTA provocation test continues to be widely used, and e majority of children with BPb 25-40 μg/dL with negative prov- ation tests do not receive chelation therapy; (3) No common proach for the treatment of Pb toxicity appears to exist; and,) In the majority of pediatric centers current management of BPb evation does not appear to reflect new information regarding e effects and treatment of Pb poisoning.

ho Needs The Lead (Pb) Mobilization Test (LMT)? lood Pb As the Sole Determinant of eed for Treatment

. E. Markowitz and J. F. Rosen

epartment of Pediatrics,
lbert Einstein College of Medicine,
nd Montefiore Medical Center, Bronx, NY

The Centers for Disease Control have recommended that the valuation of children with moderate Pb poisoning (blood Pb ≥25 nd ≤55 ug/dl and erythrocyte protoporphyrin ≥35 ug/dl*) in- lude the LMT to determine which children will respond to a ourse of chelation therapy with an enhanced Pb diuresis. How- ver, few medical centers are equipped to perform this test in ither its 24 hour in-hospital or 8 hour out-patient forms. As a esult, many children with moderate Pb poisoning may not be eceiving optimal therapy. To determine if selection criteria for helation treatment could be simplified, we analyzed the rela- ionship between blood Pb and LMT outcomes in 179 previously ntreated children with moderate Pb poisoning. After a blood sample for repeat Pb measurement was obtained, each child received a 500 mg/m^2 dose of CaNa$_2$EDTA, i.m., followed by an 8 hour urine collection for urinary Pb determination. The correlation between blood Pb and the ratio of urinary Pb to dose of EDTA (uPb^r) was .6399, p <.001. Of 28 children with blood Pb levels >40 ug/dl 23 had uPb^r ≥.70, indicating a likely benefit from chelation with CaNa$_2$EDTA. Of 22 children with blood Pb levels <25 ug/dl on the day of the LMT, none had a uPb^r ≥.70. We conclude that in circumstances where the LMT cannot be performed, children with blood Pb concentrations >40 be chelated empirically because of the likelihood of responding to CaNa$_2$EDTA (82%). Previously untreated children with blood Pb levels <25 need not undergo a LMT.

*(Pb μg/dL)/20.7 = Pb μmol/L; (EP μg/dL)/56.3 = EP μmol/L

Can We Influence Parents Whose Preschooler Has Been Recently Poisoned to Take Preventive Precautions?

A. D. Woolf, A. Saperstein, and S. Forjuoh

Department of Pediatrics,
Harvard Medical School, Boston, Mass;
Division of General Pediatrics,
Children's Hospital, Boston;
and Massachusetts Poison Control System

Among the 960,000 poisonings of children under 6 yo recorded by US poison centers annually, up to 20% will have a repeat poisoning episode before they turn 6 years old. We investigated the prevention practices of families whose preschool child had experienced a recent poisoning incident. Of 906 families queried, 336 (38%) did not have syrup of ipecac on hand one week after the poisoning incident. The families without ipecac were randomly assigned to receive (E1; N = 169) or not receive (C1; N = 167) a mailed intervention from the poison center. The intervention consisted of telephone stickers with the poison center's number, a slide cabinet lock, a coupon for $1 off the purchase price of ipecac, pamphlets on poisoning prevention, a 9-step checklist for poison-proofing the home, and a cover letter. The unit cost of the intervention packet was $2.87 (includes coupon redemption and postage). All families received a structured telephone interview 3 months after the intervention. Over 90% of enrolled families completed the follow-up. The groups were demographically comparable; these families were predominately white, middle class, and well educated. E1 families were more likely to have a poison control sticker than C1 families (78% vs 39%; $\chi^2 = 60.92$; p<0.0001) and were more likely to have in use at least one slide lock on their home cabinets (59% vs 40%; $\chi^2 = 10.8$; p<0.001). However E1 families, who had received a coupon for ipecac, were no more likely to have ipecac on hand 3 months later than those who had not (57% vs 52%; p = ns). There were no differences between groups in their implementation of other advice offered in the "9 steps." We conclude that, even after a preschooler's poisoning, parents are often not motivated to undertake poisoning prevention strategies on their own. A mailed intervention can be effective if it removes barriers to compliance with poisoning prevention advice.

Gender Difference in Health Care Utilization By Children Away From Parental Influence

M. C. J. Rudolf and A. J. Alario

Department of Pediatrics, Rhode Island Hospital,
Brown University, Providence

The increased morbidity and use of health services by women is usually explained by social and biological differences in adult life. In order to explore gender differences in the pediatric age group, infirmary utilization was studied at a residential summer camp where parental influence is at a minimum. Campers were classified according to frequency and necessity of infirmary visits. These were graded by infirmary staff, blind to the study purpose as major, minor or trivial (agreement among investigators = 88%, weighted kappa 0.63, P<0.001).

398 campers aged 8-18 years (F:M ratio 1.1:1) made 498 visits (1.5 visits/girl vs 1.0/boy, P<0.005). 237 campers used the infirmary of whom 142 were girls (P<0.01). No gender difference was seen in those visiting for major medical problems, e.g febrile illness (5% of all girls vs 4% of boys) or in those admitted (15% of girls vs 13% of boys). However a difference was seen in those visiting for minor and trivial purposes (63% of girls vs 48% of boys, P<0.05) and particularly in those making multiple (3+) visits for minor/trivial problems (21% of girls vs 11% of boys, P<0.02). There was no correlation between age and frequency of visits. Gender differences were particularly evident in those visiting for minor musculoskeletal trauma (F:M ratio 1.6:1, P<0.05) and skin trauma (1.9:1, P<0.01). Girls were no more likely than boys to involve a counselor in the decision to visit, (49% vs 43%) nor more likely to receive treatment for trivial visits (33% vs 30%) suggesting that staff were not favoring girls and encouraging return visits.

Although obvious morbidity was no different in campers, girls used the infirmary more than boys in a manner similar to that reported for adult health behavior. This suggests that gender differences occur earlier than suspected and are not simply related to adult social roles.

Barriers to Influenza Vaccination in Children with Asthma

P. G. Szilagyi, L. E. Rodewald, J. Savageau,
L. M. Yoos, and C. B. Doane

Department of Pediatrics, University of Rochester (NY)
School of Medicine and Dentistry

The AAP recommends influenza vaccination for children with moderate or severe asthma, yet few such vaccinations are provided annually. There may be several barriers to vaccination. Many providers lack a computerized database that can identify children with asthma for annual vaccination. Patient barriers may include (1) health beliefs about asthma and influenza vaccination and (2) "control" beliefs about whether their behaviors affect health status. This study examined both provider and patient barriers at a pediatric continuity clinic in an urban teaching hospital.

A computerized database identified 124 children who had a significant asthma attack within the prior year. Patients were randomly assigned to either a study group (N = 63), who were sent a personalized letter reminder about the need for an influenza vaccination, or to a control group (N = 61), who received no reminder. Study group mothers were interviewed 2 months after the letter was sent so that potential factors predicting compliance with influenza vaccination could be assessed. Questions included (1) the four major dimensions of the Health Belief Model and (2) the Multidimensional Health Locus of Control Scale (MHLC).

Eighteen study group patients (29%) and only four control patients (7%) received an influenza vaccination [$\chi^2 = 10.3$; df = 1; p<0.01]. Forty-three study group mothers were interviewed; 14 (33%) of interviewed mothers had complied with influenza vaccination recommendations. The 20 patients not interviewed had a similar vaccination rate, but could not be reached because of lack of phones, clinic visits or current addresses. Two measures correlated with vaccination compliance: high levels of parental worry about asthma, which increased compliance (odds ratio = 23.3, p<0.01) and high levels of parental worry about vaccine side effects, which decreased compliance (odds ratio = 0.087, p = 0.025). Variables not predicting compliance included: socioeconomic status, asthma severity, perceived influenza susceptibility or vaccination benefits, physical barriers to care (e.g., transportation), or results of the three MHLC instrument subscales (Internal, Powerful Others, Chance).

We conclude that (1) a computerized database is useful in recalling children with asthma for influenza vaccination; (2) although reminders increase compliance, only a subset of parents will respond to personalized letter reminders; (3) parental worry is an important intervening variable affecting compliance; and (4) assessment of parental worry may allow physicians to tailor parental education to increase influenza vaccination rates.

GENERAL PLENARY SESSION
Thursday, May 2, 8 AM-NOON

Managed Care for New York Medicaid Children: Cost Analysis of Referred Services

T. D. Sullivan

Department of Pediatrics, SUNY at Buffalo (NY),
and The Children's Hospital of Buffalo

The Children's Medicaid Program (CMP) is a State and County sponsored ongoing (5/1/87-4/30/91) demonstration project in prepaid, capitated, case-managed care for Erie Co. N.Y. Medicaid children. A cost analysis for the first 24 months presented at the 1990 APA Annual Meeting showed a decrease in overall costs despite an increase in primary care costs. The object of this study was to see if this trend has continued through 36 months and to more closely analyze referred services costs.

CMP pediatricians received a monthly fee (ranging from $8.34 to 42.47 and varying by age and sex) to provide primary care to a group of Medicaid eligible children. Most referred services with some exceptions (ER, dental) required pediatrician approval. CMP costs were compared to costs for a similar comparison group (CG) of Erie Co. Medicaid children using data from New York's computerized payment system. Participation was measured in eligible months (EM). One child in the program for 1 month equalled 1 EM. At 24 months there were 13,861 CMP EM's and 996,024 CG EM's. By 36 months EM's had more than doubled to 28,135 while CG EM's had risen to 1,515,045.

Primary care costs per EM continued to be higher for CMP children compared to the CG ($12.31 vs. $9.14, p<.001) although the gap has narrowed ($14.91 vs. $8.94, p<.001). Referred services costs per EM were much higher for the CG as follows:

	CMP	CG	p Value
Inpatient Hospital	$ 4.74	$ 9.46	<.001
Specialty MD/Clinic	2.89	7.47	<.001
Emergency Room	2.75	4.62	<.001
Pharmacy	.61	2.49	<.001
Lab/Radiology	.58	.44	<.01
Other	.15	1.06	<.001
Total	11.72	25.54	<.001

Money invested in a sound primary care system pays dividends later in decreased costs for referred services.

The Efficacy of Non-Invasive In-Hospital and Outpatient Management of Febrile Infants: A Four Year Experience

M. D. Baker, L. M. Bell, and J. R. Avner

Divisions of General Pediatrics, Emergency Medicine,
and Infectious Diseases,
The Children's Hospital of Philadelphia (Pa)

Since 1987, we have prospectively studied the safety and cost-effectiveness of non-invasive in-hospital and outpatient management of well-appearing febrile infants. Four hundred twenty-five infants 29-56 days old with rectal temperatures in excess of 38.2°C presenting to the CHOP Emergency Department were enrolled. Following a complete history, physical examination, and sepsis work-up, each child was assigned to one of three groups. In hospital controls (IHC, N = 250), were those children with either laboratory or clinical parameters suggestive of serious infection. The remaining 175 well-appearing infants with normal laboratory parameters were randomly selected for either in-hospital observation without treatment (IHO, N = 92), or outpatient observation without treatment (OPO, N = 83), but with repeat physical examinations at 24 and 48 hours. Serious illness (SI) occurred in 116

.3%) of 425 infants. SI included: meningitis, sepsis, UTI, pneu- nia, cellulitis, and bacterial gastroenteritis. One hundred fif- n of 116 children with SI were identified by our admission eria (sensitivity = 99.1% [95% CI = 95.3% - 100%]). The neg- ve predictive value was 99.4% (95% CI = 97.0-100%). One ld, in the IHO group, subsequently was diagnosed with ec- lermal dysplasia and had persistently positive blood cultures. mpared to IHC, substantial savings were realized in both IHO d OPO groups. Average medical charges were: $5,653 (IHC), 947 (IHO), and $716 (OPO). Our data indicate that using strict ection criteria, it is possible to safely and cost-effectively man- e febrile one-two month old infants without initial antibiotic atment in either the in-hospital or outpatient setting. Further- ore, outpatient management results in significant savings in tient charges.

creased Growth Velocities in ildren Living in Shelters

D. Courtlandt, A. H. Fierman, B. P. Dreyer,
Hick, D. Arnold, E. Keating, and N. Mann

epartment of Pediatrics,
ew York (NY) University School of Medicine

We have previously demonstrated in a cross sectional study at homeless children have linear growth delays when com- red with national standards and domiciled poor children. In is study, we examined the growth over time of children living a NYC homeless shelter with an on-site medical clinic and itrition supplementation programs. We collected height data, e, sex, and ethnicity from the records of all children between o and eight years of age who had routine physicals on two casions, six to eighteen months apart (N = 69). All were Med- aid eligible. Height z-scores were determined using the CDC nthropometric Software Package. Height velocity z-scores ere determined using the Genentech Growth Calculator™, hich corrects the z-score for growth intervals of less than one ear. Both programs define z-scores according to the National enter for Health Statistics (NCHS) standards.

Height velocity z-scores were significantly skewed toward gher values when compared with the expected NCHS distri- ution (chi-square goodness of fit, <.0001). The median height elocity z-score was +1.0, with 25/69 (36%) children having eight velocities >2 SD above the mean. After controlling for age, ex, ethnicity, growth time interval, and season, there was a sig- ificant negative correlation between the initial height z-score nd the height velocity z-scores (semipartial r = −.27; p = .02). hildren with the lowest initial height z-scores thus had the high- st growth velocities; however, even those with normal to high itial height z-scores had elevated height velocities (see Table).

	Height z-score				
	<−2	−2 to −1	−1 to +1	>+1	Total
Height velocity z-score (mean)	+4.07	+2.02	+0.89	+0.97	+1.36
N	6	11	40	12	69

Homeless children, especially those with the lowest initial eight z-scores, exhibited catch-up growth while in the shelter ystem. This may be due to improved access to WIC and other upplemental food programs in shelters, and supports the need or on-site nutrition programs in homeless shelters.

The Prediction of Preschool Behaviour Problems From Temperament and Other Variables in Infancy

F. Oberklaid, A. Sanson, R. Pedlow, and M. Prior

Department of Ambulatory Paediatrics,
Royal Children's Hospital, Parkville, Victoria, Australia

Difficult temperament in infancy has consistently been shown to be associated with concurrent behavioural problems (BPs) such as excessive crying, sleep difficulties and colic. However conflicting results of previous studies have resulted in uncertainty about the relationship between difficult temperament in infancy and reported problem behaviours later in childhood. In this study we utilised data from a large, representative community cohort (Total N studied = 1583) to determine if we could predict difficult preschool behaviour problems (at age 4-5 years) from difficult temperament and other variables in infancy.

In addition to global ratings of their infant's temperament (MOR), mothers completed the Revised Infant Temperament Questionnaire (RITQ) (Carey & McDevitt), a 4 point rating scale of infant behaviour problems (BPs)—excessive crying, sleep problems and colic—and provided sociodemographic data, and maternal and child health nurses globally rated the infant's temperament on a 5 point scale (NOR). Preschool behaviour problems were defined as a score greater than 1 SD above the mean on the Preschool Behaviour Questionnaire (Behar & Stringfield).

Maternal ratings of difficult temperament on the RITQ predicted only 17.5% (NS) of those with preschool behaviour problems, a percentage not significantly greater than the 14% of the total sample rated as having problems. There was some improvement in prediction when difficult temperament was added to other variables such as male sex (28%, p<.05), and low socioeconomic status (24%, p<.001). However MOR was a more powerful predictor of preschool behaviour problems, both alone (26.0%, p<.005) and in combination with other variables such as perinatal stress (36.8%, p<.01), male sex (29.5%, p<.005), non-Australian parent (29.4%, p<.05). Similarly maternal reports of infant BPs was a more powerful predictor of preschool behaviour problems both alone (21.8%, p<.001) and in combination with male sex (24.6%, p<.001), low socioeconomic status (26.1%, p<.001), non-Australian parent (21.8%, p<.01), and NOR (21.9%, p<.05). The best consistent predictor of later problems was the combination of MOR and BPs (27.0%, p<.001) and especially when combined with other infant variables such as perinatal stress (35.3%,m p<.05), male sex (31.5%, p<.001), and non-Australian parent (30.0%, p<.05).

We conclude that difficult temperament in infancy, as traditionally conceptualised and measured on the RITQ, is not on its own significantly associated with behaviour problems at 4-5 years of age. Of far greater importance for clinicians is the significant relationship between preschool behaviour problems and maternal *perceptions* of difficult temperament and behaviour in infancy. Discrepancies between detailed ratings and global perceptions of temperament in infancy may indicate stresses in the parent-child relationship which are ultimately more predictive of problems than difficult temperament *per se*.

Vaccine Storage Errors in Pediatric Practice: The Tip of an Iceberg?

D. M. Bishai, S. Bhatt, L. T. Miller, and G. F. Hayden

Department of Pediatrics,
Cedars-Sinai Medical Center, Los Angeles, Calif,
and University of Virginia Health Sciences Center,
Charlottesville

Recent increases in measles and mumps activity and the occurrence of illness among vaccinees have prompted questions about the adequacy of vaccine handling in pediatric practice. To evaluate this potential problem, we visited 46 pediatric offices (selected randomly from a list of practitioners affiliated with a metropolitan hospital), 3 hospital-based clinics, and 1 community clinic. A questionnaire was administered to the person in each office taking primary responsibility for the care of vaccines (the vaccine coordinator or VC), and each vaccine refrigerator was inspected according to a standard protocol.

The VC was neither a physician nor a nurse in 23 (46%) offices; a written description of his vaccine-related duties was infrequently available (12 offices or 24%). Only 8 (16%) VCs could cite appropriate storage temperatures for vaccines. Nine (18%) VCs were unaware that heat can harm certain vaccines, and 18 (36%) did not know that freezing can likewise be harmful. A thermometer was kept in the refrigerator in only 18 (36%) offices; the temperature was checked at least weekly in only 10 (20%) offices. On inspection, the temperature was inappropriately high (>8 deg.C) in 11 (22%) refrigerators. More than half of the refrigerators contained one or more of: outdated vaccine (62%); >1 opened vial of the same type of vaccine (52%); an opened vial which had not been dated (70%); and food or drink (62%). Vaccines were often observed on the door shelf (46%) and outside the refrigerator in uninsulated trays (16%).

Errors in vaccine handling were encountered at an alarmingly high frequency. Pediatricians should follow the guidelines for optimal vaccine storage to minimize the potential for vaccine failure among their patients.

Use of the Fentanyl Lollipop for Analgesia During Painful Procedures in Children

N. L. Schechter, S. J. Weisman, M. Rosenblum,
P. L. Conard, B. Bernstein, C. Bartolotta, C. San Antonio,
B. Shapiro, D. Cohen

Departments of Pediatrics and Anesthesia,
University of Connecticut Health Center, Farmington;
St Francis Hospital and Medical Center, Hartford, Conn;
and Children's Hospital at Philadelphia (Pa)

For many children with chronic illness, the painful procedures associated with their disease are worse then the disease itself. To address the need for rapidly-acting, safe oral analgesia and sedation for children undergoing painful diagnostic and therapeutic procedures, we examined the efficacy of oral transmucosal fentanyl citrate (OTFC) commonly known as the fentanyl lollipop in a double-blind, placebo-controlled randomized clinical trial. This preparation which is absorbed through the buccal mucosa offers a more rapid onset of action than oral medications and avoids the discomfort of intravenous cannulation or intramuscular injection.

Fifty-eight children with cancer (aged 3-17 years) scheduled for bone marrow aspiration, lumbar puncture, or central venous line removal were randomized to receive either a placebo lollipop or OTFC (17.5 mcg/kg). Children were instructed to suck on the ollipop until it was finished. The procedure was performed approximately 20 minutes later. One hour after the procedure was completed, the nurse, all children over 8, and the parent were asked to rate the pain associated with the procedure using 1-10 visual analogue scale. Children 3-7 years used the Oucher yielding a 1-6 score on both scales, 1 represents no pain.

RESULTS:	Mean Pain Rating		
	Placebo	OTFC	P
Nurse	4.1±2.0	2.8±2.0	0.01
Children			
(3-7)	4.1±1.7	2.5±1.6	0.01
(over 8)	4.7±2.5	2.1±1.9	0.007
Parent	5.3±2.7	3.2±2.2	0.003

As is evident, OTFC afforded significant reductions in discom- ort as assessed by the nurse, child, and parent. Side effects were equent but not disabling and included itching (60%) and nausea nd/or vomiting (30%). One child experienced oxygen desatu- ation but remained alert and required only stimulation.

IMPLICATIONS: This study suggests that OTFC offers the apid onset of safe analgesia via a pleasant route. It may well have pplicability to other settings such as emergency departments. offers an excellent analgesic alternative for children who require ainful procedures.

he CBC Revisited: A Bayesian Reappraisal

S. Kramer, S. M. Tange, E. G. Mills, and M. L. Bernstein

epartments of Pediatrics and of
pidemiology and Biostatistics, McGill University
culty of Medicine, Montreal, Quebec

Previous studies of the value of the CBC in distinguishing viral om bacterial infection in young febrile children have failed to clude children with clinically evident bacterial infection and us have inflated the positive predictive value of the test for occult focal infection. We prospectively studied 2844 children 3 to 24 months of age who presented to a children's hospital emergency department between March 1989 and August 1990 with fever (≥38.0°C) of acute (≤4 days) onset but no evident bacterial focus of infection, 541 (19%) of whom received a CBC. We also carried out an 8-year retrospective analysis to provide data (prior probabilities, CBC results) on rare occult bacterial infections (meningitis, osteomyelitis, septic arthritis, and enteritis).

Prior probabilities for the four most common diagnostic categories were: viral, .932; UTI (≥10^4 organisms/ml), .060; pneumonia (based on "blind" reading by a pediatric radiologist), .008; and bacterial meningitis, .00005. The likelihood of WBC ≥15,000/mm^3 was 30, 60, 57, and 50% for viral, UTI, pneumonia, and meningitis, respectively, yielding significantly ($P<.001$) elevated likelihood ratios (LR's) (relative to viral) of 1.98, 1.89, and 1.65 for the three occult infections. Among children with high WBC, neither total polymorphonuclear count ≥10,000/mm^3 nor band count ≥500/mm^3 was associated with significantly elevated LR's for any of the three occult infections, a finding confirmed by multiple logistic regression analysis. Based on the prior probabilities and likelihoods of WBC ≥15,000/mm^3 for each diagnosis, the revised (posterior) probabilities were: viral, .874; UTI, .112; pneumonia, .014; and meningitis, .00008. Thus a high WBC count approximately doubles the overall probability of occult focal bacterial infection; even then, however, a viral diagnosis remains far more likely. The increase in probability given a high WBC count is clinically important only for UTI, for which an equally sensitive and far more specific test (i.e., the urinalysis) is readily available. These results seriously undermine the diagnostic value of the CBC in the young febrile child.

Clinical Risk Index for Bacterial Meningitis Among Febrile Children

R. Lembo, D. Krowchuk, and P. McCarthy

Department of Pediatrics,
Yale University, New Haven, Conn, and
Department of Pediatrics, Case-Western Reserve University
at MetroHealth Medical Center, Cleveland, Ohio

We have previously reported a multivariate model to assess risk of bacterial meningitis (BM) among febrile children. To translate this model into a clinical instrument suitable for risk assessment, we derived a weighted numerical index based on 3 predictor variables (meningeal signs [MS], physician impression of toxicity [TOX], and the ratio of immature-to-total neutrophils [ITR] in peripheral blood) from a sample of 223 children (median age: 3 months; prevalence of BM: 20%) and then validated its diagnostic efficacy in an independent sample of 171 consecutive children (median age: 3 months; prevalence of BM: 3%) undergoing a lumbar puncture as part of an evaluation of fever.

Predictor variables were identified by logistic regression analysis. MS were considered as a binary variable (any present = 1/all absent = 0). TOX was quantified retrospectively by a naive rater based on 3 clinical items (level of consciousness, color, hydration) and considered as an ordinal score (range: 0 [non-toxic] to 15 [highly toxic]. The ITR was considered as a decimal value (range: 0.0 to 1.0). The weights represented the exponentiated beta coefficients derived from the logistic regression equation. The risk index was computed as the sum of the products of the weight times the value for each variable (numerical range: 0 to 117 points).

Subjects with BM in the derivation and validation samples had a significantly ($p<0.01$) higher median index (55.2 and 65.3 points) then did children without BM (16.6 and 10.6). The ability of the index to differentiate subjects with and without BM, as assessed by the area (c) under the receiver operating characteristic curve, was high in both samples (c = 0.86 and 0.99; perfect differentiation: c = 1.0). At a threshold value of 21 points, the index's sensitivity, specificity and predictive accuracy for BM were 0.91, 0.61, and 0.37 in the derivation sample, and 1.00, 0.70, and 0.09 in the validation sample. Raising the threshold value incrementally to 50 points maintained sensitivity at 1.0 but increased specificity to 0.96 and predictive accuracy to 0.42 in the validation sample.

We conclude that this numerical index based on data readily ccessible in the acute care setting and easily computed with a and-held calculator is of value to clinicians for objectively as- essing risk of BM in febrile children.

andomized Trial of Laxatives n the Treatment of Encopresis

. Nolan, G. Debelle, F. Oberklaid, and C. Coffey

epartment of Paediatrics and Ambulatory Paediatrics,
niversity of Melbourne, Royal Children's Hospital,
ictoria, Australia

Management of encopresis involves the use of laxative med- ation and behavior modification aimed at promoting toileting egularity. There has never been an adequate controlled evaluation of the additional benefit conferred by laxatives. A total of 69 children with encopresis and radiographic evidence of stool ccumulation were randomized to either multimodal therapy MM—laxatives plus behavior modification; n = 83), or to behav- ur modification alone (BM; n = 86). Treatment failure was de- ned as failure to achieve substantial progress towards remission y at least 6 weeks from study entry (BM group). This occurred 32 cases (37%). These subjects were deemed to have reached study end-point at the time treatment failure was declared. ean follow-up was 55.1 (sd 26.96) months for the MM group, nd 56.7 (sd 31.97) months for the BM group. Remission and nprovement rates at follow-up were—n(%):

	Remission			Remission/Partial Remission		
Group	3mo	6mo	12mo	3mo	6mo	12mo
MM (n=83)	32 (39)	41 (49)	42 (51)	39 (47)	50 (60)	52 (63)
BM (n=86)	18 (21)	26 (30)	31 (36)	21 (24)	31 (36)	37 (43)
P-value	0.019	0.017	0.079	0.004	0.003	0.016

The MM group came into remission significantly sooner than e BM group, and the difference in the Kaplan-Meier remission urves was most striking in the first 30 weeks of follow-up =.012). Separate hazard functions were modelled for llow-up prior to and subsequent to 26 weeks (phase I & II). After variate adjustment, the phase I hazard ratio was 1.91 (MM/BM, 5% ci 1.18, 3.09; p = .008). However, the hazard ratio was not gnificantly different for phase II (1.02, 95% ci 0.46, 2.26; p = .95). here were nearly identical patterns of compliance with toileting both treatment groups, although about 1 in 8 children overall id not comply with the sitting program. The BM group children ho complied poorly (n = 11) did significantly worse than all oth- s overall (p = .016). After removal of the poor compliers in both eatment groups from the dataset (n = 24), there was no signif- ant difference between BM and MM groups in phase I (hazard tio 1.49, 95% ci 0.90, 2.47; p = .12) or in phase II (hazard ratio 73, 95% ci 0.32, 1.70; p = .46). More multimodal therapy subjects perienced at least 1 relapse (33/55, 51%) than did BM group atients (17/46, 37%), but the 14% difference was not statistically gnificant (p = .21, 95% ci on difference −5%, 33%). Only 1 BM bject had more than 1 relapse, compared to 6 MM subjects. hese results demonstrate a clear advantage overall for the use laxative medication, but also show that compliant patients may st as successfully be managed without medication.

aternal Emotional State and Infant Behaviour: re They Related?

. R. Miller and R. G. Barr

epartment of Pediatrics,
ontreal (Quebec) Children's Hospital

Laboratory studies have demonstrated a relationship between inical maternal depression and infant behaviour. To determine emotional distress in otherwise-healthy first-time mothers is lated to infant crying, 88 mother-infant pairs were studied pro- ectively in their homes. At 35 weeks gestation and 6 weeks stpartum, mothers completed the General Health Questionnaire 30 (GHQ), a measure of non-psychotic emotional perturbation, plus Pitt's Pre/Postpartum Anxiety-Depression Scale and Spielberger's State Anxiety Inventory. These measures were highly intercorrelated (r's .68 to .82) so GHQ was used as the primary measure. Infant cry and fuss duration (C/F-dur; hours/day) and frequency (C/F-freq; bouts/day) were obtained from a validated diary kept by mothers for the infant's sixth week. Diary "quality", scored for detail, clarity, completeness and flaws by a rater unaware of maternal emotional state, was not related to pre- or postpartum emotions (both r's <.08, p's >.5).

RESULTS: *Prenatal* GHQ was not associated with infant C/F parameters (both r's <.07, p's >.5). In contrast, *postnatal* GHQ was associated with C/F-freq (r = .28, p <.01) and especially C/F-dur (r = .45, p<.001). Postpartum GHQ retained importance in multiple regression models incorporating significant covariates (mother's age, infant birthweight, feeding type, one parent in home, etc), accounting for 8% of variance in C/F-freq [F(4,83) = 6.2, p<.001] and 31% of C/F-dur [F(3,84 = 16.9, p<.001]. *Changes* in maternal distress from pre- to postpartum periods were examined. Infants of mothers whose scores increased on at least 2 of the 3 measures cried more (2.9 ± 1.4 hrs/day; n = 24) than those whose scores decreased (2.1 ± .9 hrs/day;n = 50) or did not change (2.2 ± 1.1 hrs/day; n = 14)[F(2,85) = 5.6, p = .005].

CONCLUSIONS: Though unrelated to prenatal emotions, crying in 6 wk-olds is related to concurrent maternal emotional distress and changes in emotional state, independent of background influences and quality of maternal diary records. Causal interpretations of this relationship must, however, remain speculative.

Perinatal Injuries: Why Families File Suit

G. B. Hickson, E. W. Clayton,
P. B. Githens, and F. A. Sloan

Vanderbilt Institute for Public Policy Studies,
Health Policy Center,
Vanderbilt University, Nashville, Tenn

It is assumed that following perinatal injuries, families need money to provide care for their children and therefore file suit. Yet, it is likely that reasons for filing may be more complex. To examine this possibility, Florida families (n = 169) identified from a random sampling of closed claims filed between 1978 and 1989, were asked to participate in a one hour interview and provide written consent for release of pertinent medical records to investigators; 127 (75%) agreed. Families offered 179 responses to the question, "Why did you file suit?". These responses were categorized by two independent reviewers who achieved 91% agreement for category assignments. Reasons for filing included: advised to sue by influential others (32% of families), believed a cover-up existed (24%), needed money (23%), child had no future (23%), wanted to find out what happened (20%), and revenge (19%). Reasons for suit were evaluated with respect to potential discriminant variables (family characteristics, medical experiences). Predictors for "advised to sue" included being told by a medical professional that care offered had caused injury (F = 13.9, p<.01) before the family recognized that a problem existed (F = 7.9, p<.01). Predictors for "belief in cover-up" included the perception that a physician tried to mislead (F = 18.3, p<.01), failed to mention the existence of a long term problem (F = 7.6, p<.01) and offer NICU care (F = 6.5, p<.01). "Needed money" was predicted by knowing before birth there might be a problem (F = 5.7, p<.02) and previous contact with a lawyer (F = 4.9, p<.03). "Needed information" was predicted by the perception that an M.D. was unwilling to talk (F = 16.4, p<.01), while the desire for "revenge" was predicted by a child's death (F = 15.0, p<.01), belief that an M.D. would not listen (F = 7.4, p<.01), and overhearing a medical conversation (F = 3.28, p<.07).

Families express reasons for suit other than simply the need for dollars. A no-fault system might meet monetary needs, but would not necessarily provide families with information and a public forum to express distress, frustration and anger with the medical profession.

Maltreatment of Young Children Born to Teenage Mothers: A Comparison Between the Late 1960's and the Early 1980's

C. S. Rude, J. M. Leventhal,
S. M. Horwitz, and D. M. Stier

Departments of Pediatrics and
Epidemiology and Public Health,
Yale University School of Medicine, New Haven, Conn

Despite a marked increase in reported cases of child maltreatment, controversy exists about whether this represents an actual increase in child maltreatment or simply increased reporting. To examine this question, we studied two cohorts of children born at Yale-New Haven Hospital (YNHH) to Black mothers who were <19 years old at the time of delivery. One cohort was enrolled from 9/67-6/69 ($N = 148$) and the other from 10/79-12/81 ($N = 159$). Information about each child's first five years of life was obtained from medical records at YNHH and at the three other major health care facilities providing care to these children. Two pediatricians independently rated each reported injury as accident, maltreatment (abuse, sexual abuse, or neglect), or insufficient information using predefined criteria. Disagreements between reviewers were resolved by consensus.

There were no statistically significant differences between the two cohorts ('60's vs. '80's) in terms of maternal age (mean = 16.6 years for both groups), male gender (56% vs. 55%), low birthweight (10% vs. 11%), prematurity (11% vs. 5.6%, $p = 0.11$), 5 minute Apgars <8 (8.3% vs. 5.9%, $p = 0.42$) and neonatal complications (11.5% vs. 18.2%, $p = 0.10$). There was, however, a lower rate of Title 19 enrollment in the earlier group (88% vs. 95%, $p < 0.05$). The mean number of injuries per case in the two cohorts was similar (1.59 vs. 1.65), as was the percentage of cases with ≥ 1 accidents (49.3% vs. 59.7%, $p = 0.07$). There was no significant difference in the percentage of cases with maltreatment between the two cohorts (14.9% vs. 10.7%, $p = 0.27$). In the earlier cohort, there was a significantly greater percentage of cases with insufficient information recorded in the chart about certain events (17.6% vs. 5.0%, $p < 0.005$).

These results indicate that when the events of the two cohorts are examined using the same criteria, there is no difference in the rates of maltreatment in children in teenage mothers from the 1960's to the 1980's. We suggest that the marked increase in reporting is likely due to better recognition rather than to true changes in the frequency of maltreatment over time.

Author Index to APA Abstracts

air, R. 405
re, F. 391, 409
rio, A.J. 401, 417
xander, D.T. 388
nquist, J.R. 389
derman, C.R. 413
derson, A.B. 390
derson, B. 400
bel, A. 407
nold, D. 419
ner, J.R. 416
isden, K. 394
ker, M.D. 418
ll, L. 402
rbaresi, W. 384
rlow, B. 385
rnett, S. 387
ron, M. 397
rr, R.G. 396, 404, 421
rrett, K. 405
rthel, M.J. 385
rtolotta, C. 420
skin, M.N. 390
tes, A.S. 414
uchner, B. 397
uchner, H. 405, 408, 417
um, J. 394
hrman, A.J. 386
ll, L.M. 418
ll, S. 398
ncivenga, K. 397
nincasa, G. 407
rensen, A. 387
rgman, A.B. 391
rgman, D. 391
rkelhamer, J.E. 399
rkowitz, G. 412
rman, S. 403
rnstein, B. 420
rnstein, M.L. 420
att, S. 419
ro, F.M. 387
shai, D.M. 419
thoney, W.G. 384, 386
londis, T.A. 391
radley, R.H. 405
rayden, R.M. 395
razdziunas, D. 411
rotherton, S. 391
rown, B.C. 396
alderon, C. 399
allahan, C.M. 384, 395
ampbell, J.R. 389
artland, J.D.C. 395
asey, P.H. 405
asey, R. 398
etta, F. 389
hapman, J. 397
harney, E. 384
hernoff, R.G. 392
hristensen-Szalanski, J. 407
hristoffel, K.K. 416
icchetti, D. 397, 410
icchetti, D.V. 410
lark, G.D. 384
lausen, C. 401
layton, E.W. 421
offey, C. 421
ohen, D. 420
onard, P.L. 420
otton, B.C. 396
ourtlandt, C.D. 407, 419
ox, J.E. 386
oyne, L. 386
rain, E.F. 400
ross, A.W. 397
unningham, S.J. 400
zarkowski, N. 397
avenport, M.G. 404
Davidson, L.L. 385
Davidson, N. 383
Davis, A.T. 403
Davis, H.W. 409
Davis, J.K. 394
De Jong, A.R. 383, 386
de Triquet, J.M. 401
DeAngelis, C. 415
Debelle, G. 421
DelBeccaro, M.A. 400
DeMarzo, S. 402
Dennehy, P.H. 401
Dennison, B.A. 401
Desilets, J. 404
DiBrigida, L.A. 406
DiPasquale, K.J. 390
Doane, C.B. 389, 418
Dougherty, G.E. 388, 402
Doughman, J.A. 387
Dreyer, B.P. 407, 419
DuBerger, R. 404
Dubowitz, H. 383, 406
Duggan, A.K. 415
Dungy, C. 391, 407
Durkin, M.S. 385
Dusdieker, L. 391
Dwyer, D. 408
Earp, J.A. 399
Ekwo, E. 411
Ellis, S.P. 394
Evans, A.E. 414
Feigelman, S. 383, 406
Feinstein, R.A. 396
Feldman, W. 403
Field, C. 395
Fierman, A.H. 407, 419
Fink, H. 397
Fleisher, G.R. 390
Foch, B.J. 396
Forjuoh, S. 417
Forrest, C.B. 415
Forsyth, B.W.C. 397, 405, 408
Fowler, M.G. 404, 413
Francoeur, T.E. 396, 404
French, J. 393
Fried, L.E. 413
Friedland, L.R. 409
Gaar, G.G. 390
Garabedian, C. 408
Garg, R. 404
Githens, P.B. 421
Glotzer, D. 417
Goldstein, M. 392
Gonzalez, G. 399
Gortmaker, S.L. 415
Gosselink, C. 411
Gould, J.H. 400
Graef, J.W. 416
Grant, T.M. 384
Griffin, P. 412
Grisanti, K.A. 388
Grisso, J.A. 415
Grose, K. 403
Grossman, D.C. 398
Grossman, L.S. 392
Guzman, M. 406
Halfon, N. 412
Hamilton, J.P. 410
Hayden, G.F. 419
Heagarty, M.C. 385
Heery, L.B. 395
Hermosa, B. 394
Herrera, L. 394
Herrera, M. 403
Hershman, S.J. 393
Hick, K. 419
Hickson, G.B. 421
Holtrop, T. 408
Hong, C.H. 396
Hope, S. 383
Horwitz, S.M. 384, 386, 393, 396, 405, 408, 422
Howard, B. 384
Hubbard, T.W. 401
Huber-Navin, C. 403
Ihnat, D.H.K. 410
Inglis, A.F. 401
Ireys, H.T. 393, 397
Irigoyen, M. 392
Irons, T.G. 403
Isaacman, D.J. 409
Jackson, E. 397
Jaffe, D.M. 388
Jarman, F.C. 411
Jaudes, P.K. 411
Jekel, J.F. 396
Joffe, M. 409
Johnson, D.R. 404
Jones, M. 398
Kaplan, E.L. 404
Kappelman, M.M. 392
Karasic, R.B. 409
Katchan, B. 396
Keating, E. 419
Kelleher, K. 405
Kelly, B. 398
Kelly, B.A. 388
Kelly, D. 398
Kemper, K.J. 407
Kerns, D.L. 409
Kirby, R. 395
Klee, L. 412
Klerman, L.V. 396
Koeber, C. 397
Korsch, B.M. 406
Kouri, E. 410
Kowaleski, K.R. 402, 412
Kramer, M.S. 390, 412, 420
Kresheck, A. 411
Krowchuk, D. 420
Krug, S.E. 410
Lannon, C.M. 399
Lavelle, J.M. 387
Leaf, P.J. 393, 405, 408
Leduc, D. 396, 404
Lee, L.H. 389
Lehmann, M. 411
Lembo, R. 420
Lempert, R. 414
Levenson, S. 405
Leventhal, J.M. 386, 393, 405, 408, 410, 422
Lewander, W.J. 401
Li, M. 402, 412
Lichenstein, R. 383
Lieu, T.A. 390
Long, T.J. 410
Losch, M. 407
Luberti, A.A. 383
Lubitz, D.L. 410
Lustman-Findling, K. 397
Mann, N. 407, 419
Mansell, A.L. 401
Marble, R.D. 410
Margolis, P.X. 414
Markowitz, M.E. 417
Marshall, J. 408
Martone, M. 411
Martorell, R. 394
Maurer, J.T. 385
McCarthy, P. 397, 420
McConnochie, K.M. 415
McCormick, D.P. 387
McGillivray, D. 388, 390
Meert, K. 408
Melman, S. 414
Mendelman, P.M. 401
Mendoza, F. 394
Meropol, S.B. 383
Metcalf, T.J. 403
Miles, C.G. 415
Miller, A.R. 421
Miller, L.T. 419
Mills, E.G. 420
Mungo, R. 406
Murph, J. 391
Murph, W. 391
Nachtsheim, B. 403
Needlman, R.D. 413
Negrete, V. 406
Neifert, M. 402
Neuspiel, D. 414
Newacheck, P.W. 399
Newman, T.B. 383
Nolan, T. 421
Nosal, T. 395
Novack, A.H. 384, 389
Nuss, R. 403
Nypaver, M. 403
O'Connor, P. 385
Oberklaid, F. 419, 421
Oberlander, T.F. 388
Oh, M.K. 396
Okun, A. 392
Olsen, R.D. 400
Olson, A.L. 406
Palevsky, L. 407
Pantell, R. 391
Pascoe, J.M. 393
Pedlow, R. 419
Pelham, T.L. 400
Perrin, J.M. 415
Pew, M.C. 386
Philipp, B. 405
Phipps, P. 384
Pichichero, M.E. 389
Pless, I.B. 388
Pliskin, N.H. 399
Polansky, M. 414
Pope, S. 405
Prieto, L.R. 409
Prior, M. 419
Raisys, V.A. 384
Reising, S.F. 387
Reyes, I. 387
Richardson, M.A. 401
Ritter, M.L. 409
Rivara, F.P. 395, 398
Roark, R. 403
Roberts-Brauer, R. 390, 412
Rodewald, L.E. 389, 418
Rogers, J.E. 389
Roghmann, K.J. 389, 415
Roizen, N.J. 391
Roncevich, S. 410
Ros, S.P. 389
Rosen, J.F. 417
Rosenberg, A.J. 413
Rosenblum, M. 420
Roter, D. 406
Rotman, A. 396, 404
Rude, C.S. 422
Rudolf, M.C.J. 417
Russell, D. 407
Ryan, A. 384
San Antonio, C. 420
Sanders, J.K. 416
Sanson, A. 419
Saperstein, A. 417
Sarnaik, A. 408
Savageau, J. 418
Schechter, N.L. 420
Schiffrin, A. 402
Schneider, R. 410
Schorr, S. 414
Schwartz, J.S. 390
Schwartz, R.M. 391
Schwarz, D.F. 415
Seacat, J. 402
Seifer, R. 401
Senturia, Y.D. 416
Serwint, J.R. 406
Shannon, M.W. 416
Shapiro, B. 420
Shaw, K.N. 386, 387
Shelov, S. 414
Sher, L.D. 403
Shofer, F.S. 386
Siegel, D.M. 394
Silver, E.J. 393, 397
Simms, M.D. 384
Simpson, G.A. 413
Sloan, F.A. 421
Smith, M.B.H. 403
Snellman, L.W. 404
Soderberg, R.W. 398
Soulen, J.L. 415
Speechley, K.N. 393, 405
Squittieri, C. 407
St Peter, R.F. 399
Stang, H.J. 404
Stang, J.M. 404
Starr, M.C. 411
Stein, M. 391
Stein, R.E.K. 392, 394, 397
Stevenson, D.K. 383
Stier, D.M. 422
Stout, J.W. 413
Streissguth, A.P. 384
Sullivan, T.D. 418
Swanson, M. 405
Szilagyi, P.G. 389, 418
Sznajderman, S. 397
Takata, G. 394
Talarico, C. 410
Tange, S.M. 420
Tanz, R.R. 385
Taylor, J.A. 389, 410
Tepper, V. 383, 406
Teuscher, A.M. 416
Theodorou, A. 408
Valcarcel, M. 399
Vandeven, A. 384
Verhulst, S. 398
Vinci, R. 408
Waring, E.R. 416
Wasserman, D.R. 410
Weisman, S.J. 420
Weiss, J.C. 383, 400
Weitzman, M.L. 415
Welshimer, K.J. 397
Werner, M.J. 395
Whitehead, T. 413
Whiteside, L. 405
Wiley, C.C. 398
Wiley, II, J.F. 409
Wilkinson, G. 387
Willenborg, A. 414
Williams, R. 412
Wilson, M.E.H. 385, 406
Wissow, L.S. 385, 406
Wolfson, V.M. 415
Woodin, K.A. 389
Woolf, A.D. 417
Yaremko, J. 396, 404
Yoos, L.M. 418
Young, P.C. 403
Zanga, J.R. 416
Zellman, G.L. 385
Zieserl, E. 403
Zondorak-Perez, M.E. 394
Zuckerman, B.S. 405, 413
Zuravin, S. 383, 406

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All photographs in which there is a possibility of patient identification should be accompanied by a signed statement of consent from both parents (or guardians). Covering eyes to mask identity is not sufficient.

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Journal articles: Bier DM, Fulginiti VA, Garfunkel JM, et al. Duplicate publication and related problems. *AJDC.* 1990;144:1293-1294.

Books: Naeye RL. How and when does antenatal hypoxia damage fetal brains? In: Kubli F, Patel N, Schmidt W, Linderkamp O, eds. *Perinatal Events and Brain Damage in Surviving Children.* New York, NY: Springer Verlag NY Inc; 1988:83-91.

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1991 Annual Meeting

The annual meeting of The American Pediatric Society, The Society for Pediatric Research, and The Ambulatory Pediatric Association will be held April 29 through May 2, 1991, at the New Orleans (La) Hilton and Rivergate Convention Center. For further information, contact the APS/SPR Association Headquarters, 2650 Yale Blvd SE, Suite 104, Albuquerque, NM 87106; (505) 764-9099; FAX (505) 842-8227; or the Ambulatory Pediatric Association, 6728 Old McLean Village, McLean, VA 22101; (703) 556-9222.

Diphtheria and Tetanus Toxoids and Pertussis Vaccine Litigation

Sir.—Orenstein's letter,[1] published in the May 1990 issue of *AJDC*, points out what is naive and bad in current thinking concerning litigation over the diphtheria and tetanus toxoids and pertussis vaccines. The National Vaccine Injury Compensation Program, effective October 1, 1988, was the most naive, if not the most stupid attempt at controlling a segment of our legal system that needs to be controlled. Intended to offer a good method of avoiding costly legal battles, it did just the opposite. Lawyers now have two recourses to sue. They can always sue if the National Vaccine Injury Compensation Program is not to their liking.

For the private sector, the program did nothing but increase our cost of the vaccine to approximately $17 per dose (not the $7.96 the government pays).

Numerous studies have indicated that the vaccine itself had nothing to do with the "brain damage" reported by attorneys and parents. Because the availability of these vaccines is in the public interest, the government and the infectious disease "moguls" should take a firm stand supporting the safety of these vaccines. Those who claim a child was damaged by the vaccine should show that similar outbreaks occurred among recipients of the same "batch" of vaccine. If this is not proven, and other malpractice is not shown, no million-dollar settlements should be made. At most, I advocate providing facilities and funds to care for the affected children on an ongoing basis. Without these requirements of proof, we will be "overcharging" continually for essential vaccines. The legal profession has caused this excessive expense. There is no medical justification to it, and as soon as the truth is told, maybe an end to this problem will be achieved. Crossing our fingers or eating garlic will not keep the vampires from their litigation. We need a wooden stake!

Howard Lokietz, MD
Arcadia Medical Arts Bldg
624 W Duarte Rd, Suite 104
Arcadia, CA 91006

1. Orenstein WA. DTP vaccine litigation, 1988. *AJDC*. 1990;144:517.

In Reply.—The author did not wish to respond. I have a great deal of interest in this area, however, and thought that a response to Dr Lokietz' letter was important.

I do not agree with his assessment of the National Vaccine Compensation Program and its implementation. Having participated in the defense of physicians and others in vaccine-related litigation, I can attest to the harm that the tort-system handling of these claims has for everyone concerned. In my view, substitution of the compensation method for adjudicating claims of vaccine-induced injuries is a far better method than the adversarial legal method.

Initially, an agreement on what would be included in the Vaccine Injury Table,[1] which is the source for determining the applicability of a given claim, was the only way that the system could work. That the table will need refinement in the future is clear. That not everyone accepts "brain damage" as a consequence of pertussis vaccine is also clear, as my recent editorial points out.[2] Some insist that such an association is causal and true. A national debate that could alter the entries in the Vaccine Injury Table is now under way. This is an evolutionary process, and time to effect change is to be expected, since the scientific establishment has long considered central nervous system damage a rare consequence of administration of pertussis vaccine. To overturn that viewpoint simply by declaring it not to be so is naive.

One of the problems with the democratic system is that change is cumbersome and requires extensive negotiation, persuasion, examination of facts and myths, and sorting of fact from myth, with ultimate resolution, often with compromises. On the other hand, I know of no other system that works as well as the democratic one, so I will continue to work within it, doing my part to effect change, when change is indicated.

Vincent A. Fulginiti, MD
Editor, *AJDC*

1. Committee on Infectious Diseases, American Academy of Pediatrics. *1988 Red Book*. Elk Grove Village, Ill: American Academy of Pediatrics; 1988:531-534.
2. Fulginiti VA. A pertussis vaccine myth dies. *AJDC*. 1990;144:860-861.

Antibody Response to MMR Vaccination in Children Who Received IVIG as Neonates

Sir.—The administration of intravenous immunoglobulin (IVIG) to

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This department of *AJDC* is reserved for comment, criticism, observation, and discussion of issues of current concern and importance for children's health. The Editor encourages our readers to express themselves on a variety of topics and issues. Further, we encourage the submission of unique and brief clinical and scientific observations that do not fulfill the criteria for original articles.

Gestational Age (GA), Birth Weight (BW), No. of Intravenous Immunoglobulin (IVIG) Infusions, and Total IVIG Dose Given to Five Infants Later Studied for IgG Antibody Response to Measles, Mumps, Rubella (MMR) Vaccination

GA, wk	BW, g	No. of IVIG Infusions	Total IVIG Dose, g	Rubeola IgG*	Mumps IgG*	Rubella IgG*
27	535	5	5.9	0.43	2.93	4.14
26	890	3	5.4	0.40	4.81	3.54
28	1150	3	5.4	0.41	1.85	3.88
31	1000	3	3.9	0.62	1.67	5.01
30	1500	1	1.6	0.44	4.00	3.45

*Reference ranges (enzyme immunoassay units) for IgG response to MMR are as follows: rubeola, >0.16; mumps, >0.9; and rubella, >1.5. They represent the means + 3 SDs for 150 normal people, as stated by the manufacturers of the enzyme immunoassay kits used (rubeola and mumps from Whittaker Bioproducts Inc, Walkersville, Md; rubella from Pharmacia Diagnostics Inc, Fairfield, NY).

neonates has few or no acute short-term effects,[1] but less is known about the subsequent effect on humoral immune function. We studied the response to measles, mumps, rubella (MMR) vaccination in five children who received multiple infusions of IVIG during the neonatal period.

We obtained serum from five children who had participated in a study of IVIG pharmakokinetics in infants of 32 weeks' gestation or less weighing 1500 g or less in the Cedars-Sinai Neonatal Intensive Care Unit, Los Angeles, Calif.[2] The Table shows the gestational age and birth weight of each infant, the number of IVIG infusions, and total IVIG dose. These infants were subsequently vaccinated against rubeola, mumps, and rubella at 15 months of age. Serum samples were obtained 2 months after vaccination. The Table also shows the IgG response to MMR vaccination with reference ranges. Following vaccination, normal amounts of IgG antibodies were found in all children. There was no evidence of recent immunologic response to rubeola, mumps, or rubella as manifested by the absence of specific IgM antibodies to these viruses.

Our data indicate a normal response to MMR vaccination 15 months after IVIG infusion. Results of another study of 19 infants weighing less than 1500 g at birth who received one 1-g dose of IVIG for prophylaxis against acquired cytomegalovirus infection confirm the normal antibody response to MMR.[3] Our five infants received repeated doses of IVIG during hospitalization necessary to maintain protective IgG levels. Thus, the response to MMR appears to remain intact following larger IVIG doses. Our results are encouraging because the use of IVIG is increasing in both investigations and in the community.

Jeanne W. Ruderman, MD
Division of Neonatology
Ahmanson Department of Pediatrics
Cedars-Sinai Medical Center
Los Angeles, CA 90048
Noori Barka, PhD
James B. Peter, MD, PhD
Specialty Laboratories Inc
Santa Monica, CA 90404
E. Richard Stiehm, MD
Division of Immunology
Department of Pediatrics
UCLA School of Medicine
Los Angeles, CA 90024

1. Christensen RD, Hardman T, Thornton J, Hill HR. A randomized, double-blind, placebo-controlled investigation on the safety of intravenous immune globulin administration to preterm neonates. *J Perinatol.* 1989;9:126-130.
2. Ruderman JW, Peter JB, Gall RC, Stewart ME, Pomerance JJ, Stiehm ER. Prevention of hypogammaglobulinemia of prematurity with intravenous immune globulin. *J Perinatol.* 1990;10:150-155.
3. Berzen A, Whyte H, Chabot J, Roifman C. Treatment with gammaglobulin in newborns does not affect subsequent humoral immune function? *Pediatr Res.* 1990;27:262. Abstract.

Vaccine Myth and Physician Handouts

Sir.—I read with interest the editorials by Cherry[1] in the March 23/30 1990 issue of *JAMA* and by Fulginiti[2] in the August 1990 issue of *AJDC* and am concerned about an issue neither physician addressed, namely, the handouts from the Centers for Disease Control that pediatricians have been strongly encouraged to give to our patients. These handouts hardly help to dispel the myth of the connection between diphtheria-pertussis-tetanus vaccine and encephalopathy.

These pamphlets not only tell parents that there is a connection, but give the approximate odds of encephalitis and permanent brain damage occurring. We have distributed these pamphlets not only to protect ourselves from the liability of failing to properly inform parents, but also to educate them about these possible problems associated with the vaccine. Now we are told the problem is all a myth. Thus, we are handing out pamphlets with misinformation. Should we continue to distribute these pamphlets and further spread the myth, or should we stop, thus leading to possible serious liability problems?

Thomas P. Lynch, MD
DuPage Pediatrics Ltd
805 Plainfield Rd
Darien, IL 60559

1. Cherry JD. 'Pertussis vaccine encephalopathy': it is time to recognize it as the myth that it is. *JAMA.* 1990;263:1679-1680.
2. Fulginiti VA. A pertussis vaccine myth dies. *AJDC.* 1990;144:860-861.

In Reply.—Dr Lynch raises an important point in regard to the diphtheria-pertussis-tetanus "Important Information" forms currently being distributed by the Centers for Disease Control.

As noted in the 1988 *Report of the Committee of Infectious Diseases* of the American Academy of Pediatrics, "The National Childhood Vaccine Injury Act (PL99-660; Amended by PL100-203), which became effective

1988 includes requirements for de-iled notification of patients/parents bout vaccine benefits and risks in oth the private and public sectors. his legislation requires develop-ent and distribution of standard-ed benefits/risk statements when dministering vaccines for which accine injury compensation is avail-le. These statements are in prepa-tion and physicians will be notified the federal government when eir use becomes mandatory." The enters for Disease Control has been orking on the new forms (*which will mandatory*), and draft editions have en reviewed by many people. At esent, members of the Vaccine Com-ission and members of the parents oup (Dissatisfied Parents Together) ve strenuously objected to attempts make the new forms reflect the level information we currently have. I do t know when new, more appropri-e forms will be available.

What to do in the interim, the ques-n posed by Dr Lynch, is intriguing. clearly is dishonest to use the present rms. However, there is no easy al-rnative. One possibility would be to ntinue to use the present forms but tell parents that the risk of neuro-gic illness and death resulting from phtheria-pertussis-tetanus immuni-tion is grossly exaggerated on the rms. If this is done, it would be wise indicate on the form and in the med-l record what information the par-ts were given.

James D. Cherry, MD
Department of Pediatrics
Division of Infectious Diseases
UCLA School of Medicine
10833 LeConte Ave
22-442-MDCC
Los Angeles, CA 90024-1752

Reply.—Dr Lynch outlines a prob-n in using the current generation of nportant Information" documents epared by the Centers for Disease ntrol, and in wide use among pe-atricians, and the need for a new neration of such statements. As Dr erry indicates in his response, we not yet there. The new set of in-mational pamphlets for patients d physicians has been in preparation some time now. The issues are con-versial and have caused delays in preparation and ultimate distribu-n of these newer statements.

Major controversy stems from the phasis to be given to adverse ef-ts of vaccines vs adverse outcomes of disease and benefits of vaccine. Most physicians, including me, believe that the data clearly support an overwhelming degree of benefit of the vaccine compared with the risk. However, a number of individual laypersons, groups of laypersons, and some physicians believe that the public is ill informed about the risks of vaccines. These persons wish to place greater emphasis on the potential adverse events, to "enlighten" the public. Unfortunately, this dispute has led to disruption of an orderly process in preparing these materials.

For example, if a vaccine can cause one death in tens of millions of doses, should that fact be trumpeted? Some persons feel that the only correct way to inform the public is by having a black box surround such data on the face sheet of any document that "informs." Obviously, many of us believe this is extreme, inaccurate, and misleading. We believe that such misrepresentation of the risk/benefit ratio would lead to disenchantment with the vaccine. Advocates of such methods fail to take into account the much larger number of deaths that would occur among those who are not vaccinated, and fight against emphasizing such data. In one debate in which I was involved, the phrase "vaccines are safe and effective, but not perfectly safe nor perfectly effective" drew considerable opposition. To me, and others, the phrase concisely sums up the issue, but to opponents of the vaccine, it is believed to deliver a message that is too optimistic and fails to warn adequately.

The debate will continue until statements can be prepared that satisfy neither party completely, but do what both parties basically want it to do. Multiply this type of discussion/debate times 100 and one begins to see the difficulty in preparing reasonable statements.

Adding fuel to such debate is the emergence of new knowledge. The issue of brain damage alleged to accompany pertussis vaccine administration is a case in point. Dr Cherry and I have attempted to point out that such causal association is a "myth," perpetuated by inaccurate reports and scientific uncertainty in the past. We have called for an end to the myth, but simply stating that position does not make it happen. Dr Lynch and his colleagues will hear a great deal more on this issue as the various advisory committees consider the scientific data, reach their own conclusions, and make recommendations. This is a time-consuming process, which means that we will not see the type of documents that Dr Lynch seeks in the near future.

Vincent A. Fulginiti, MD
Editor, *AJDC*
Dean's Office, Room 1529
Tulane University School of
Medicine
1430 Tulane Ave
New Orleans, LA 70112

Exhibitor "Giveaways": A Curmudgeon's View

Sir.—I attended the Fall meeting of the American Academy of Pediatrics in Chicago last year. Everybody seemed to love the trinkets, snacks, pens, flashlights, and other paraphernalia given away by convention exhibitors. As I watched the escalators to the exhibit hall, participants descended with only their programs in hand; but on the way up, many carried shopping bags bulging with "goodies." As listed below, most of the giveaways did not bear the slightest relationship to the products being promoted, but who cared? They were free!

Exhibitor's Product	**Giveaway Item**
Steroid cream	Book underliner
Immunoglobulin	Writing pen
Allergy medication	Instant photo
Fever control medication	Windbreaker
Sore throat spray	Coffee mug
Skin cleansing products	Rubber bath toy
Laxative	Doughnuts
Digestive enzyme	T-shirt
Sun cream	Beach ball
Pain reliever	Coffee mug
Skin ointment	Travel contest

We all know that you do not get something for nothing. The cost of these promotion items—one part of the pharmaceutical industry's multi-billion-dollar advertising expenses—are eventually absorbed by consumers, the children and families we serve. In 1988, there were 16 pharmaceutical companies listed in the Fortune 500 group of the largest industrial corporations in the United States. Their combined sales of over $61 *billion* resulted in reported profits of nearly $8.3 billion. Fifteen of the companies had higher profits as a percent of sales than General Motors (*Fortune Magazine.* April 24, 1989:354-399)!

The other price of giveaways is a more subtle one, difficult to quantify, but arguably as real. Giveaways have the potential to cloud the objective evaluation of products by physicians.[1] At the American Academy of Pediatrics meeting, an exhibitor promoting a prescription-only topical steroid enticed pediatricians to the booth by giving away book underliners and magnifying lenses. After accepting such "gifts," people are much more likely to courteously listen to the sales pitch. They are also less likely to ask pointed questions, such as, Is this steroid any more effective [probably not] or more costly [almost certainly] than plain hydrocortisone?

I think giveaways should be abolished from professional meetings. As listed below in the tabulation of starting salaries, physicians are among the highest-earning individuals in the United States.[2,3]

Occupation	**Income, $**
Physicians	85 630
Dentists	40 190
Lawyers	32 757
Registered nurses	23 443
Computer programmers	22 531
Accountants	22 198
Typists	13 538
Minimum-wage earners ($3.35/h)	6968

They would not suffer any severe effects if deprived of free coffee mugs, writing pens, or book underliners. Instead of snapping instant photographs or offering free pens, let exhibitors use their marketing dollars to describe and demonstrate products, provide and discuss scientific studies (perhaps we can see some of the "data on file" that are often cited in drug advertisements), and answer probing questions about cost, toxicity, and relative effectiveness of alternate therapies. For the pediatrician who wants objective information about a medication or therapy, there is *The Medical Letter on Drugs and Therapeutics*, a nonprofit publication that does not accept drug company advertising. The giveaway ban should include product samples. If physicians want samples, they can have them mailed to their offices. This approach would be much less wasteful, and much safer for physicians' children, who need not have access to drugs brought home from medical meetings.

Of course, there is no guarantee that companies will pass on to consumers whatever savings are realized by a ban on giveaways. Even if the cost burden on families does not become lighter, at least our carry-on luggage—and our consciences—will be.

Lawrence R. Berger, MD, MPH
Lovelace Medical Foundation
2441 Ridgecrest SE
Albuquerque, NM 87108

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New York State Health Code 405 Update

Sir.—We appreciate Bedrick's editorial comments in the August issue of *AJDC.*[1] We would like to update our experience in more recent schedule revisions. The ultimate outcome measures of the schedule must be the quality of both patient care and resident learning. One must recall that, when night call was changed by a quantum leap from every second night to every third night for interns, studies of that modification were nonexistent. Thus, we are charting new waters. We plan to carefully monitor the quality of medical care with measures addressed by the hospital and Pediatric Department quality assurance protocols. Also, board scores will be closely scrutinized and each resident's yearly improvement compared with the individual resident improvement before the "405" schedule was started.

The only objective data to be reported thus far is the observations by the faculty that (1) the residents are more alert and awake than they were in the old system, and (2) continuity has improved compared with prior schedules. It is interesting to note that we are matching for the same number of residents that we did prior to the "405" regulations. Our straight pediatric postgraduate level 1 roster has been as follows: 51 in 1987-1988; 49 in 1988-1989; 52 in 1989-1990; and 49 in 1990-1991.

While the actual total number of house staff members has remained stable, there has been a small adjustment in service commitment and a reassignment of duties internally to accomplish our overall objective.

In addition to the above, the schedule has been changed to accommodate a "night float"/floor resident team and also a "day float" senior resident. Acceptance of these new revisions has been positively received by the house staff. It does seem that there is a realistic way to make resident working hours more reasonable and humane while maintaining a high-quality learning experience and providing high-quality patient care.

Gerald E. Daigler, MD
Robert C. Welliver, MD
F. Bruder Stapleton, MD
219 Bryant St
Buffalo, NY 14222

1. Bedrick AD. The eighty-hour workweek: residency friend or foe? *AJDC.* 1990;144:857.

THE EDITORIAL BOARD SPEAKS...

Complex Problem: Complex Solutions

Elizabeth McAnarney, MD

"Lissa" continues to be a valuable addition to our editorial board. Her respected position within adolescent medicine has assisted us in the review of manuscripts, in ideas concerning features for AJDC *involving adolescent issues, and in encouraging authors to submit their work to us for consideration.Currently, Lissa serves as associate chair of Academic Affairs in the Department of Pediatrics at the University of Rochester (NY) Medical Center and continues to head a vigorous Division of Adolescent Medicine as well. She serves as chair of the department's Promotion and Tenure Committee.*

In 1990, Lissa received the Job Lewis Smith Award of the Section of Community Pediatrics, American Academy of Pediatrics, for her work in adolescent health. She also received a Distinguished Service Award from the American Medical Association at the National Congress on Youth in 1990.

Lissa is a much sought-after lecturer and most recently delivered talks at the University of Cincinnati, Ohio, and St Louis (Mo) University. She also continues her roles as mentor to fellows and as researcher; she published seven reports in 1990.

Lissa remains enthusiastic and of great help to AJDC. *Her commentary on the complex problems of adolescent pregnancy below offers some principles to serve this troubled group.*

The challenge of adolescent pregnancy has evoked responses from many sectors: society at large, religious groups, educators, health care professionals, parents, and adolescents themselves. We have every reason to engage in this dialogue, for adolescent pregnancy is one of our greatest challenges. As pediatricians, we are concerned about the health of adolescents and their children.

Adolescent pregnancy is a complex sociocultural and biologic condition. Attitudes about sexuality, sexual activity, pregnancy, contraception, and abortion are all rooted in the cultures and subcultures of our pluralistic society. The biologic capacity to reproduce is one of the hallmarks of adolescence and, for many young people, provides opportunities to fulfill lives that previously have had few accomplishments. To be close to another person (if only transiently), to attempt to prove one's femininity or masculinity by becoming pregnant or impregnating another, and/or to become a parent with new status are powerful motivators for some young people.

There may be few reasons for some young people to plan ahead, either by delaying sexual activity or, if sexually active, delaying pregnancy by using effective contraception. Adolescents, as they have in the past, will continue to become pregnant. Assuming, therefore, that adolescent pregnancy is an ongoing problem, we might ask a question similar to that asked by former New York City Mayor Edward Koch: How are they (adolescents and their children) doing? The answer to that question might be, "not too bad, but not too good."

The "not too bad" part reflects those successful prenatal interdisciplinary adolescent maternity projects that have resulted in improved short-term (ie, obstetric, neonatal, and psychosocial) outcomes as shown in several studies.[1,2] There have also been long-term, promising outcome data for the majority of mothers who were cared for in an adolescent maternity project in the late 1960s and were followed up 17 years later. The majority of these mothers had finished their educations, were not receiving public assistance, and were working at the time of follow-up.

The "not too good" part comes from data indicating distressing long-term outcomes for the children of these adolescent mothers, who themselves did so well. These children, as adolescents, had distressingly poor outcomes, eg, school failure, early sexual activity, and adolescent pregnancy.[3] In addition, the United States still has the highest adolescent pregnancy, birth, and abortion rates compared with those of other industrialized countries (the rate is expressed as the number of pregnancies per 1000 women in that age group). The following data compare the United States and the Netherlands: pregnancy rate, 109.9 vs 15.0, respectively; birth rate, 51.7 vs 7.7, respectively; and abortion rate 43.5 vs 5.3, respectively.[4]

Overall, these data, which are far from complete, indicate the complex nature of adolescent pregnancy and outcome. The solutions to adolescent pregnancy are complex; we should not promise simple panaceas for this challenging sociocultural-biologic phenomenon. Merely dedicating more financial resources to "solving" adolescent pregnancy is not the only strategy. If we articulate clear, nonjudgmental basic principles *and* follow them, adolescents and society will be well served. These basic principles might include the following:

1. It is better to delay sexual activity during early and middle adolescence and to avoid pregnancy. This principle could be supported by modeling dignity and respect between the sexes, demonstrating responsible sexual behavior, and providing decreased media attention to irresponsible sexual activity.
2. If young people become sexually active, they need to consider the consequences, not only to themselves, but also to their potential offspring and to society. Some may believe that most adolescents do not have the capacity to consider consequences meaningfully; some obviously will not be able to. Nevertheless, we must reinforce this basic principle by educating our young people in their families, schools, and health care settings about responsible sexuality. Parenthetically, we need better contraceptive methods that are independent of adolescents' behavior.
3. If a young person becomes pregnant and decides to keep her infant, she must enter prenatal care early and continue with it to optimize her outcome as well as her infant's. Other goals include returning to school to finish her education and securing the best child care possible to make sure the children have the best chance of achieving healthy futures.

If we follow these principles and perhaps others, we shall have served society and its young people honestly and consistently.

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Acquired Immunodeficiency Syndrome and Adolescents

Knowledge, Attitudes, and Behaviors of Runaway and Homeless Youths

Susan Tucker Sugerman, MD, MPH; Albert C. Hergenroeder, MD; Mariam R. Chacko, MD; Guy S. Parcel, PhD

• *Objective*: To describe the knowledge, attitudes, and behaviors of runaway and homeless youths regarding infection with the human immunodeficiency virus (HIV).
Design: Cross-sectional, descriptive.
Setting: A crisis shelter for runaway and homeless youths.
Participants: One hundred one residents, aged 13 to 20 years, of a shelter for homeless and runaway youths in Houston, Tex.
Intervention: None.
Measurements/Main Results: A self-administered questionnaire was used to examine the knowledge, attitudes, and behaviors of these youths regarding infection with HIV. Nearly one fourth had injected illegal drugs; one fifth had shared needles for other purposes. Sixteen percent had had anal intercourse, 19% had engaged in prostitution, and 67% of all subects reported having four or more sexual partners. One fifth eported that they always use condoms. While quite knowledgeable about means of transmission, they held prevalent misconceptions about casual contact and risk reduction. Youths perceive few barriers to condom use, have fairly high intenions to practice preventive behavior, and have high selfficacy to do so. Most believe they are at little or no risk for cquiring HIV. These findings support the need for medical, ducational, and social service programs to reduce the risk of HIV among these youths.
Conclusion: Runaway and homeless youths practice behaviors hat place them at high risk for acquisition of HIV infection. isk reduction is imperative and will require programs that ddress the educational, psychological, social, and medical eeds of these youths.

(*AJDC*. 1991;145:431-436)

The adolescent population in the United States represents a potential high-risk group for acquiring the human immunodeficiency virus (HIV) and subsequently suffering acquired immunodeficiency syndrome (AIDS) because of sexual activity and experimentation with illegal drugs. Although persons aged 13 to 19 years account for less than 1% of all cases of AIDS in this country, young adults between the ages of 20 and 29 years represent 20% of all reported cases.[1] As the median interval between infection and onset of AIDS is nearly 10 years,[2] it is likely that many of these young adults with AIDS acquired the infection during their teenage years.

Information available on the seroprevalence of antibodies to HIV in adolescents is limited. Studies of groups of youths and young adults have shown seropositivity rates of 0.34% among 1 141 164 teenaged youths (younger than 20 years) applying for military service,[3] 0.41% among 34 089 Job Corps entrants, and 0.2% among 12 000 college students.[4,5] Ten (0.32%) of 3124 patients tested positive for HIV antibodies at an ambulatory clinic and emergency facility for adolescents in an urban center.[6]

Seroprevalence rates among homeless and runaway youths are remarkably higher. A shelter for such youths in New York, NY, reported that nearly 7% (74/1111) of its residents tested positive for HIV antibodies.[7] A Vancouver (British Columbia) study of HIV in the homeless reported a seroprevalence of 5.4% among 92 street youths aged 14 to 19 years.[8] A shelter for homeless and runaway youths in Houston, Tex, reported that 2.1% of 864 individuals tested between October 1988 and September 1989 showed evidence of HIV antibodies (L. F. Novick, MD, PhD, written communication, December 6, 1989). Similarly, serum testing of street youths using intravenous drugs in Houston revealed a positivity rate of 2% (M. L. Williams, PhD, written communication, March 22, 1990).

While many published studies address the knowledge, attitudes, and behaviors of the general adolescent population regarding HIV infection,[9] little is known about homeless adolescents. The few investigators examining risk behaviors of homeless and runaway youths have shown high rates of heterosexual and homosexual behavIOPMr,[8,10,11] as well as prevalent anal intercourse,[8] prostitution, and drug abuse.[8,11,12] Many runaway and homeless youths have been abused sexually, suggesting another potential source of infection for these teenagers.[8,11,13]

To develop appropriate medical, educational, and social services to reduce the transmission of HIV among homeless and runaway youths, a better understanding is needed of the behavioral and psychosocial factors that

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From the Univeristy of Texas School of Public Health (Dr Sugrman) and the Center for Health Promotion Research and Development (Dr Parcel), University of Texas School of Public Health, ouston; and the Sections of Adolescent Medicine (Drs Hergenoeder and Chacko) and Academic Ambulatory Pediatrics (Dr hacko), Department of Pediatrics, Baylor College of Medicine, ouston, Tex. Dr Sugerman is currently with University of Cincinnati (Ohio) Children's Hospital Medical Center.

Reprints not available.

Table 1.—Demographic Characteristics of 101 Runaway and Homeless Youths at Shelter Facility in Houston, Tex, 1990

Characteristic	No. (%)
Sex	
F	38 (37.6)
M	63 (62.4)
Age, y	
13-14	6 (5.9)
15-16	19 (18.8)
17-18	37 (36.6)
19 or older	39 (38.6)
Race/ethnicity	
Black	29 (28.7)
White	52 (51.4)
Hispanic	12 (11.9)
Other	8 (8.0)

place this population at risk. This study examines the behaviors, knowledge, and attitudes regarding HIV and AIDS among adolescents recruited from a shelter for homeless and runaway youths in Houston.

SUBJECTS AND METHODS

Selection of Participants

This study was approved by the Committee for the Protection of Human Subjects at the University of Texas Health Science Center and the Institutional Review Board of Baylor College of Medicine, Houston.

Subjects were residents, aged 13 through 20 years, of a shelter for homeless and runaway youths who were invited to complete an anonymous, self-administered questionnaire at the shelter's clinic facility. Residents coming to the shelter clinic for any reason were invited to participate; youths in the residential buildings were invited to come to the clinic as their schedules permitted.

Verbal consent was obtained from the subjects after explaining the purpose of the study, stressing that no coding devices would be used, that names would not be recorded, and that participation was strictly voluntary. Each subject completed the questionnaire in a private room and returned it in a sealed envelope to a locked box. The principal investigator then met with each subject to answer any questions and provided them with educational pamphlets and information about HIV/AIDS counseling and testing resources.

Survey Instrument

The survey questionnaire was adapted with minor revisions from the Student Health Risk Survey by K. Basen-Engquist, PhD, and G.S.P. (written communication, November 13, 1989), which was designed to investigate knowledge, attitudes, behaviors, and various other cognitive variables regarding HIV and AIDS among high school students. To measure specific behavioral and psychosocial constructs, the questionnaire was divided into several scales made up of items specific to that variable. These scales could then be used to examine the relationships between variables associated with risk behaviors for HIV infection. Four behavior scales measured sexual activity (three questions), anal intercourse (two questions), prostitution (three questions), and needle use or exchange activities (five questions). An additional question addressed frequency of condom use. Twenty-three items determined a scale of factual knowledge regarding AIDS. Individual items addressed sources of information and testing resources. Cognitive variables derived from the Health Belief Model,[14] Theory of Reasoned Action,[15] and Social Learning Theory[16] were employed to examine perceived barriers to condom use (six questions), perceived susceptibility to HIV (two questions),[14] personal beliefs and social norms regarding sexual activity and condom use (three questions each), behavioral intentions to enact preventive behaviors (four questions),[15] and self-efficacy to perform preventive behaviors (13 questions).[16]

Table 2.—Risk Behaviors for HIV Infection Among 101 Runaway and Homeless Youths at Shelter Facility in Houston, Tex, 1990

Behavior (No. Responding)	No. (%)
Sexual activity	
No. of sexual partners	
Ever (100)	
0	4 (4.0)
1	19 (19.0)
2-3	10 (10.0)
4 or more	67 (67.0)
Last year (97)	
0	13 (13.4)
1	25 (25.8)
2-3	22 (22.7)
4 or more	37 (38.1)
Age at first intercourse, y (100)	
Virgin	4 (4.0)
12 or younger	38 (38.0)
13-15	41 (41.0)
16-17	15 (15.0)
18 or older	2 (2.0)
Frequency of condom use (99)	
Virgin	4 (4.0)
Always	20 (20.2)
Sometimes	42 (42.4)
Rarely or never	33 (33.3)
Anal intercourse (98)	
Ever	16 (16.3)
Last year	15 (15.3)
Prostitution (100)	19 (19.0)
Sexual preference (males; 61)	
Virgin	1 (1.6)
Heterosexual	49 (80.3)
Homosexual	7 (11.5)
Bisexual	4 (6.6)
Needle use	
Ever injected drugs (99)	24 (24.2)
Injected in last year (98)	14 (14.3)
Shared needles for drugs (100)	12 (12.0)
Shared needles last year (100)	11 (11.0)
Shared for blood brothers, tattooing, piercing ears (100)	21 (21.0)

Another scale involved anxiety regarding interacting with persons with AIDS.

Data Analysis

Data were collected during a 3-week period ending in February 1990. Subjects' responses were entered into dBASE III PLUS[17] and subsequently analyzed using the Statistical Package for the Social Sciences (SPSS).[18] Items were examined individually and by scales where appropriate. Descriptive analysis was performed using all responses, with percentages reported excluding missing values. For χ^2 tests of independence of items, missing values were excluded pairwise. For the purpose of scale analyses, four cases were deleted because subjects left more than 20% of the questionnaire unanswered, and all scale items were counted as missing if subjects left more than 20% of that scale unanswered. Student's t tests for independence of means excluded missing values pairwise. Pearson's correlation coefficient was used to determine correlation between scale scores.

RESULTS

Of 110 residents invited, 101 agreed to participate (92% response rate), representing 46% of the 221 youths residing at the shelter at any time during the study period. One individual was excluded owing to inability to speak or understand English. Subject characteristics are reported in Table 1.

Table 3.—Scale and Reliability Scores Measuring Behavior and Cognitive Variables for 97 Runaway and Homeless Youths at Shelter Facility in Houston, Tex, 1990*

Variable (No. Responding)	Range	Mean ± SE	Cronbach's α
Sexual activity: first intercourse, No. of partners in lifetime, past year (95)	0-12	8.55 ± 0.328	.738
Anal intercourse: lifetime or past year (95)	0-2	0.305 ± 0.070	.887
Prostitution for money, drugs, place to stay (97)	0-3	0.402 ± 0.092	.862
Needle use: IV drugs or needle sharing (95)	0-5	0.853 ± 0.150	.838
Knowledge (97)	0-23	17.0 ± 0.478	.864
Personal beliefs supporting intercourse with boyfriend or girlfriend, multiple partners, sex without condoms (96)	0-12	4.65 ± 0.242	.354
Social norms supporting intercourse with boyfriend or girlfriend, multiple partners, sex without condoms (96)	0-12	6.76 ± 0.282	.517
Behavioral intentions regarding preventive behaviors (92)	0-16	9.42 ± 0.339	.626
Perceived barriers to condom use (95)	0-24	7.23 ± 0.545	.654
Perceived susceptibility to HIV (92)	0-6	2.28 ± 0.193	.835
Self-efficacy to enact preventive behaviors (86)	0-39	30.2 ± 0.773	.889
Anxiety about interacting with persons with AIDS (97)	0-12	2.87 ± 0.278	.710

*Four respondents were deleted owing to greater than 20% missing responses. IV indicates intravenous; HIV, human immunodeficiency virus, and AIDS, acquired immunodeficiency syndrome.

Risk behaviors are reported in Table 2. Scale and reliability scores measuring behavior and cognitive variables and reliabilities are reported in Table 3.

Risk Behaviors for HIV Infection and AIDS

It is evident from Table 2 that many youths are involved in high-risk behavior for acquisition of HIV infection. Based on scale scores for risk behaviors, those who had ever injected drugs or had recently shared needles for injecting drugs were more likely to have been involved in a sexual exchange for money, drugs, or a place to stay ($F=4.94$, $P<.01$; $F=3.14$, $P=.04$); likewise, those trading sex for money, drugs, or a place to stay scored higher on a scale for needle use ($F=1.73$, $P<.01$; $F=1.97$, $P<.01$; and $F=1.6$, $P<.01$). Those who reported being forced to have sexual intercourse scored higher on scales for prostitution ($F=1.69$, $P=.05$) and anal intercourse ($F=4.34$, $P<.01$).

Knowledge

On 23 questions testing knowledge regarding HIV and AIDS, subjects scored a mean of 75% correct responses. At least 86% correctly identified having sex without a condom, sharing needles or syringes, and pregnancy as means of transmitting HIV. Most subjects (72%) knew that AIDS is not transmitted by having a blood test; however, only 49% knew that it is not transmitted by donating blood, and only 31% responded that almost all transfusions are now safe. The subjects answered questions correctly about whether casual contact transmits HIV at least 85% of the time, with some exceptions: few knew that mosquitoes (47%), public toilets (69%), and coughs or sneezes (69%) do not pose risks for HIV transmission. More than one third believed they could reduce their risk by washing or urinating after sex (39% and 37%, respectively) or by making sure a sexual partner looks healthy (38%). Most knew that one cannot tell by appearances if someone has AIDS (68%), that people other than homosexual men can get the disease (84%), and that there is no cure for AIDS (78%).

Attitudes and Cognitive Variables

Regarding condom use, few had religious or moral objections to using condoms (15%) or believed that condoms make sex seem dirty (16%), and only 16% believed that using a condom to prevent AIDS is embarrassing. Twenty-six percent believed it can be important not to use a condom to show love and trust for someone, and 55% believed that condoms make sex seem planned. The majority (87%) believed that condoms probably or definitely should be used if a person is sexually active; however, only 58% believed that their peers shared this belief.

Ninety-two percent reported knowing where to get condoms. They felt certain they could get a condom if they wanted one (90%), could have it with them when they needed it (76%), and could get their partner to agree to use the condom (74%). Similarly, 74% felt confident that they could refuse sexual intercourse if their partner refused to use a condom. Less than half (32%) of those feeling confident about having a condom with them when they needed it reported actually using them always or sometimes ($\chi^2=13.76$, $P<.01$), and only 44% of those feeling confident about getting their partner to agree to use condoms reported using condoms always or sometimes ($\chi^2=5.85$, $P=.02$).

Results regarding beliefs about sexual activity indicated that 76% believed sex with a steady boyfriend or girlfriend was appropriate, and 74% believed that their peers believed the same. Of note, only 18% personally believed sex with multiple partners was appropriate, whereas 54% believed that their peers held this view.

Overall, 29% reported being worried about getting AIDS, although more female respondents (46%) reported being worried than male respondents (19%). Those who reported being worried were more likely to respond that someone had tried to force them to have sex against their will (68%) than those who were not worried (36%). More female (68%) than male respondents (28%) reported someone attempting to force them to have sex when they did not want to.

Regarding their perceived risk of getting HIV or AIDS, only 9% of the subjects viewed themselves as being at high risk for acquiring HIV; 19% believed they were at medium risk. Thirty-five percent reported themselves at low risk, and 36% believed they were at no risk at all. When asked about their risk at some future time (age 21 years), the numbers of those who predicted themselves to be at high, medium, and low risk increased to 17%, 18%, and 38%, respectively; 28% predicted that they would be at no risk in the future. Among those who predicted themselves to be at high risk for HIV infection in the future, only 29% reported using condoms always or sometimes.

Regarding their intentions to practice preventive behaviors to protect themselves from HIV infection and AIDS, 31% responded that they would abstain from sex, 22% were not sure, and 48% probably or definitely would not refrain from sex. Sixty-eight percent said they would talk with their partners about HIV and AIDS before deciding whether or not to have intercourse; 85% felt confident they could do this. Fifty-two percent said they would always, and 24% said they would sometimes discuss using condoms with their partners before deciding whether or not to have sex; 88% felt sure they could do the same. Fifty-one percent intended always to use condoms when having sex, and 27% intended to use them sometimes. Female respondents were more likely than male respondents to intend to practice preventive behaviors ($F=1.16$, $P=.01$).

On the whole, subjects felt little anxiety about interacting with persons with AIDS. Only 4% said they would stop being friends with someone with AIDS; 7% said they would be afraid to hug a friend who had AIDS. Few believed persons with AIDS should be kept away from others or would mind being in the same room as someone with AIDS (8% and 9%, respectively). More were worried about catching AIDS in a public restroom (35%) and reported they would be afraid to kiss a boyfriend or girlfriend who had AIDS (31%).

While more subjects reported having talked with a friend (81%) than an adult (60%) about HIV and AIDS, most believed they knew where to get information about AIDS (71%) and how to avoid acquiring HIV (93%). Two thirds (67%) reported knowing where to get tested for antibodies to HIV.

Correlations of Scale Score

Scale analysis showed a significant positive correlation between prostitution and needle use ($r=.316$, $P<.01$). Anal intercourse was weakly correlated with needle use as well ($r=.214$, $P=.04$). Increased sexual activity was weakly correlated with prostitution ($r=.198$, $P=.05$) and with decreased intention to practice preventive behavior ($r=-.354$, $P=.001$). Prostitution was inversely correlated with intention to practice preventive behaviors ($r=-.227$, $P=.03$). Increased social anxiety about interacting with persons with AIDS was correlated with increased barriers to using condoms ($r=.441$, $P<.001$). While behavior was not associated significantly with knowledge, increased knowledge was correlated with decreased anxiety about interacting with persons with AIDS ($r=-.409$, $P<.001$) and with decreased barriers to condom use ($r=-.531$, $P<.001$). Increased self-efficacy to enact preventive behavior was found to be correlated with decreased anxiety ($r=-.307$, $P<.01$), decreased barriers to condom use ($r=-.426$, $P<.001$), and decreased perceived susceptibility to AIDS ($r=-.243$, $P=.03$).

COMMENT

This study confirms that homeless and runaway youths engage in behavior putting them at increased risk for acquiring HIV infection. The rate of intravenous drug abuse, rate of needle sharing among drug users, number of sexual partners, and rate of prostitution reported herein compare with results in other studies of runaways, street youths, and crack users.[6,8,11,12,19] The rate of intravenous drug abuse, however, is much higher than that of American high school students, reported to be between 1%[20] and 6.3%.[21] It is difficult to make an exact comparison of the number of sexual partners reported in this study with numbers in college and high school studies, as investigators report the number of partners according to varying parameters.[21,22]

Reported rates of anal intercourse in this study must be interpreted with caution, as several subjects inquired about the meaning of the term "anal intercourse." It may be that others also were unclear about its meaning and did not ask. Noting this, the rate of anal intercourse found in the study sample is similar to rates reported for inner-city black and Hispanic youths, other homeless youths, and black college students[8,23-25] and higher than reported for college women (9%).[22]

While many of the subjects are at high risk for acquiring HIV, participants perceive themselves to be at less risk than adolescents surveyed in other studies. Fewer than 10% of the subjects in this study view themselves at high risk now, and 17% believe they will be at high risk in the future. The reason for the perception of low risk is unclear, but one may speculate that survival on the street gives these youths a false sense of security and perceived invulnerability.

These youths are knowledgeable about high-risk behavior for the transmission of HIV but understand less about the low risk of casual contact and about blood products. These results are similar to those of other adolescent HIV/AIDS knowledge surveys.[21,25-29] The misunderstandings about oral contraceptives, washing after sexual intercourse, urinating after sexual intercourse, and choosing partners who look healthy indicate that myths about reducing risk of acquiring HIV infection persist despite high levels of factual knowledge regarding other aspects of HIV and AIDS. The media and medical communities should work together to reinforce the facts and dispel the myths.

This study found no relationship between knowledge and behavior but did find significant relationships between increased knowledge and decreased perceived barriers to condom use and between increased knowledge and decreased social anxiety about interacting with persons with AIDS. The latter two findings are encouraging and suggest that knowledge may be associated with more favorable beliefs and behaviors. The low anxiety about interacting with people with AIDS may have been influenced by the presence of an HIV-infected individual residing at the shelter shortly before the study period. This person was open about the diagnosis, which led to much discussion about HIV and AIDS among the residents.

The number of youths in this study who always or sometimes use condoms is similar to numbers reported in other studies on homeless and runaway youths,[8] Massachusetts teenagers,[26] and males at an urban health center.[30] It seems that these youths know the value of condoms in preventing the spread of AIDS, know where to get them, and feel omfortable using them when they need to. This information suggests that lack of information about condoms r access to them may not be the primary cause of their ctual failure to use condoms. Rather, it may be related to ne decision to use condoms at the time of intercourse. Counseling on how to use the condom during moments f sexual intimacy may improve condom use.

Significant discrepancies were noted between subject's personal beliefs about sexual behavior and their perceptions of their peers' beliefs about sexual behavior and condom use. This information suggests that perceived peer opinion may be more influential than personal beliefs in determining behavior for these adolescents. Weinstein's[31] heory of optimistic bias may also partly explain the discrepancy between perceived peer beliefs and personal beefs. He observed that college students consistently beeved that their actions, life-styles, and personalities were more advantageous than those of their peers and were apable of keeping their thoughts about their own behavior and their vulnerability in quite separate mental compartments. Educational efforts should therefore take into consideration the perceived norms for behavior and strategies used to develop norms more consistent with lowerisk behavior. In addition, educational efforts need strongly to emphasize the link between behavior and susceptibility, stressing that youths who engage in high-risk behavior need to see themselves as the ones most likely o suffer harm.

Scale analysis proved useful in determining associations and correlations among factors that may contribute to the risk status of these youths. Of particular note, subjects scored high on the scale for self-efficacy to enact preventive behavior, a finding that contrasts sharply with their reported behaviors. It is paradoxical also that those who are least confident both of their ability to have condoms when necessary and to get partners to use condoms actually reported using them more often than those who are more confident. One could hypothesize that their reported self-efficacy to enact preventive behavior is a reflection of their highly developed survival skills as runaways.

Study Limitations

Because subjects were not recruited using random probability techniques, results may be subject to bias. Youths with full-time day jobs or those attending school participated in the study before or after these other commitments but may have been underrepresented. While closely representative of gender and age distributions noted among shelter residents in 1989, this sample may be disproportionately overrepresented by whites (51.5% in this study vs 32.8% in 1989) and underrepresented by blacks (28.7% in this study vs 45.3% in 1989).[32]

The self-reporting of risk behaviors, which could not be independently verified, represents a potential source of bias in this and any study investigating behavior associated with acquisition of HIV. However, all efforts were made to provide confidentiality and anonymity to encourage subjects to represent their behaviors accurately.

Conclusion

This study describes a population whose knowledge and attitudes are inconsistent with their high-risk behaviors. Programs are needed to help these youths develop more realistic perceptions of their susceptibility. Also, more research is needed regarding the factors that contribute to condom use at the time of intercourse and on how behavioral intentions translate into actions. The relative impact on behavior of social norms vs personal beliefs deserves further investigation. The relationship of self-efficacy to behavior warrants more study as well.

As suggested by their prevalent risk behaviors and substantiated by seroprevalence studies, homeless and runaway youths are vulnerable to acquiring HIV infection. Efforts aimed at protecting these youths from HIV should also help slow the spread of the disease generally, as intervention may be more efficiently directed toward a smaller subgroup with known risks than toward a larger population with fewer risks. Unfortunately, homeless and runaway youths may be among the most difficult to access, as their life-styles cause them to be disfranchised from conventional medical and social services. Public health efforts to stop the spread of the disease among them should take advantage of and expand on existing resources that reach these youths, including shelter facilities, street outreach programs, food pantries, community health clinics, and other social service agencies. Furthermore, serious efforts should be directed toward understanding the determinants of their homelessness, such as dysfunctional family situations, home sexual abuse, poverty, and poor education. Taking steps to alleviate these conditions should help prevent these youths from adopting the behaviors that place them at risk for acquiring HIV infection.

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Article

The Total Iron-Binding Capacity in Iron Poisoning

Is It Useful?

Milton Tenenbein, MD, FRCPC, FAAP, Randall W. Yatscoff, PhD, FCACB

Traditionally, a serum iron concentration in excess of the otal iron-binding capacity (TIBC) is considered as an indication for deferoxamine therapy in acute iron poisoning. We observed a reversible elevation of the TIBC in patients with ron poisoning that coincided with their acute hyperferremia and have hypothesized that this is a laboratory aberration. We tested this hypothesis in vitro and found that the addition of iron to test serum samples produced a related increase in he TIBC, and alteration of the assay by providing additional adsorbent prevented this occurrence. We also evaluated the eproducibility of the TIBC as performed by 500 laboratories on 10 different reference samples. The mean coefficient of variation was 16%, which was unsatisfactory. We concluded hat the TIBC should not be used in the decision for the iniiation of deferoxamine therapy in acute iron poisoning. Furhermore, high TIBC values that are occasionally seen in patients with iron poisoning should not be considered as providing a protective effect.

(AJDC. **1991;145:437-439)**

A serum iron concentration greater than the total iron-binding capacity (TIBC) is often cited as a criterion for he initiation of deferoxamine therapy in patients with iron poisoning.[1] This recommendation is attractive because it ssumes that the binding of iron to plasma proteins preents toxic damage. Our review of the literature could not nd data that support this practice; however, we did find hat this recommendation coincides with the commercial vailability of deferoxamine.[2] We have observed several patients with iron poisoning with TIBC determinations hat are above the reference range and that return to normal with a fall in the serum iron concentration (Table). An unusual TIBC in a patient with hyperferremia has been documented by others.[3] We designed the following experiments to test the hypothesis that this elevation of the IBC is a laboratory aberration and not a true event.

MATERIALS AND METHODS

An automated analyzer (Du Pont aca, Du Pont Inc, Wilmington, Del) was used for the serum iron and TIBC measurements. The manufacturer's method for measuring serum iron was followed, and the magnesium carbonate method of Ramsay[4] (100 mg of magnesium carbonate) was used for measuring the TIBC (Fig 1, top). Tests were done in the hospital service laboratory that participated in the Wellcome General Clinical Chemistry Quality Assessment Program (Wellcome Diagnostics, Division of the Wellcome Foundation, London, England).

Four experiments were performed as follows: (1) Test serum samples were spiked with iron to final measured concentrations of 52 to 1560 μmol/L (286 to 8560 μg/dL), and TIBCs were quantified. (2) Test serum samples were spiked with iron as ferrioxamine to final calculated concentrations of 0 to 1000 μmol/L, and TIBCs were quantified to determine if ferrioxamine interfered with the measurement of the TIBC. (3) Two pools of test serum samples were spiked with 10 and 100 μmol/L (55 and 550 μg/dL) of iron. To each, serial dilutions of deferoxamine mesylate were added in concentrations of 0 to 500 μmol/L, and TIBCs were quantified to determine if deferoxamine interfered with this assay. (4) Experiment 1 was repeated with twice the amount of magnesium carbonate. Pooled human serum obtained from the Canadian Red Cross Blood Bank, Winnipeg, Manitoba, were used throughout. Deferoxamine was obtained from a manufacturer (Ciba-Geigy Canada, Mississauga, Ontario), and ferrioxamine was prepared in house by combining equimolar amounts of stock iron with deferoxamine. The concentration of ferrioxamine was confirmed by its absorbability at 435 nm, ie, its absorption maximum. All experiments were done in triplicate, and mean results are presented.

We also assessed the interlaboratory reproducibility of the TIBC measurement under conditions of normoferremia. We chose the results for 10 random samples from 500 laboratories that submitted values for the TIBC to the Wellcome General Clinical Chemistry Quality Assessment Program. We calculated the mean coefficients of variation of the TIBC determinations for each of the 10 submitted specimens performed by these laboratories.

RESULTS

The results of experiments 1, 2, and 4 are shown in Fig 2. For illustrative purposes, we have only included iron concentrations of 0 to 600 μmol/L (0 to 3300 μg/dL). The trends continue to be unchanged beyond this range, and the clinically relevant concentrations are included within it. The TIBC began to rise when the serum iron concentration exceeded 72 μmol/L (396 μg/dL) and consistently rose in a nonproportional fashion. This was not observed with the addition of iron as ferrioxamine (experiment 2) or with the addition of deferoxamine to serum samples that were previously spiked with iron (experiment 3). The

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From the Departments of Pediatrics (Dr Tenenbein), Medicine Drs Tenenbein and Yatscoff), and Clinical Chemistry (Dr Yatscoff), niversity of Manitoba, Winnipeg, and The Manitoba Poison Conol Centre, Winnipeg (Dr Tenenbein).

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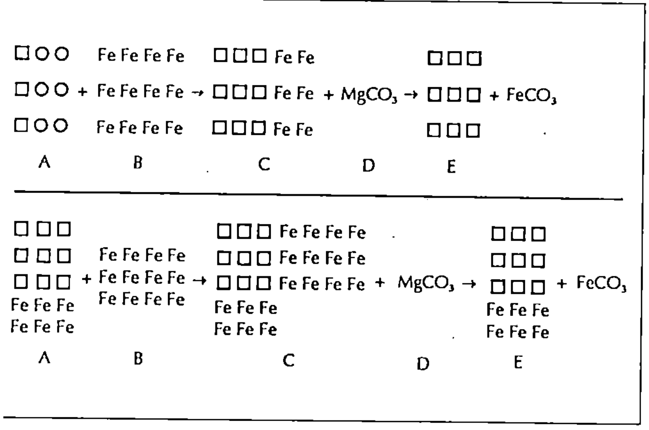
Reprint requests to Children's Hospital, 840 Sherbook St, Winipeg, Manitoba, Canada R3A 1S1 (Dr Tenenbein).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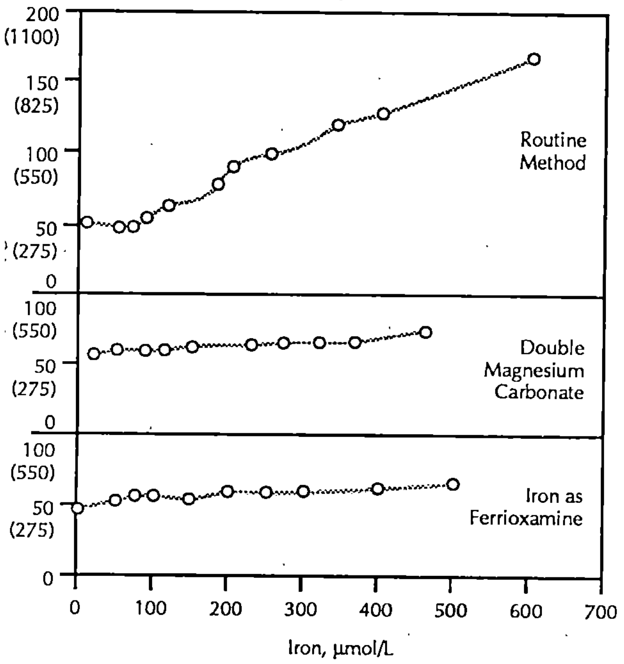
ig 1.—*Top, Measurement of the total iron-binding capacity in the ormal patient. To the patient's serum (A), a standard amount of xogenous iron (B) is added. This occupies all of the binding sites nd produces a mild excess of unbound iron (C). To this, a standard mount of magnesium carbonate ($MgCO_3$) (D) is added that forms omplexes with the unbound iron (E). After centrifugation, the iron the supernatant is measured, that is the total iron-binding ca- acity. Bottom, Measurement of the total iron-binding capacity in he patient with iron poisoning. In this situation, the binding sites re totally saturated, and exogenous iron is present (A). Addition of he standard amount of excess iron (B) creates a situation of massive nbound iron (C). This exogenous iron, along with the ingested on, overwhelms the capacity for complexation by the routine mount of $MgCO_3$. Because centrifugation only removes the iron arbonate complexes, the subsequent iron assay measures both the ound and free iron (E), thus overestimating the total iron-binding apacity. Squares indicate bound iron; circles, binding sites; Fe, free on; and $FeCO_3$, iron carbonate.*



2.—*Total iron-binding capacity (TIBC) vs serum iron concentra- n. Top, The TIBC begins to rise at serum iron concentrations 2 μmol/L (396 μg/dL). Center, Doubling the amount of magne- m carbonate largely ablates this observation. Bottom, Iron as fer- xamine does not affect the TIBC.*

Serum Iron Concentrations and TIBCs in Four Patients With Iron Overdose*

Patient	Hours After Overdose	Serum Iron Concentration, μmol/L (μg/dL)	TIBC, μmol/L (μg/dL)
1	5	1631 (8970)	560 (3080)
	8	958 (5270)	244 (1344)
	24	44 (244)	47 (256)
2†	2	108 (594)	114 (627)
	7	76 (418)	90 (495)
	8	57 (314)	87 (479)
3	3	83 (457)	81 (446)
	7	72 (396)	69 (380)
	15	42 (231)	63 (347)
4	3	95 (523)	87 (479)
	6	540 (2970)	159 (875)
	10	281 (1546)	123 (677)
	26	44 (242)	57 (314)
Normal range	...	8-24 (44-132)	45-72 (250-400)

*TIBCs indicates total iron-binding capacities.

†This patient was treated with deferoxamine, and she produced orange urine, indicating the presence of ferrioxamine.

addition of twice the amount of magnesium carbonate (experiment 4) largely ablated the increase of the TIBC. However, minor increases of approximately 30% to 40% were still observed when the serum iron concentration was greater than 225 μmol/L (1238 μg/dL).

Our evaluation of the results of the 10 random samples from the Wellcome General Clinical Chemistry Quality Assessment Program found coefficients of variation that ranged from 11.8% to 21.4%, with a mean of 16%. For a TIBC of 60 μmol/L (325 μg/dL), this represented a 95% confidence interval of 41 to 79 μmol/L (221 to 429 μg/dL), which is clearly too broad a range to be acceptable as a criterion for initiation of deferoxamine therapy.

COMMENT

Unreliability of the TIBC has previously been mentioned,[3] and we have found other examples of abnormally elevated TIBC values, albeit uncommented on, in published series of patients with iron poisoning. In one study, there were five patients with TIBC determinations greater than 90 μmol/L (495 μg/dL), with the highest being 212 μmol/L (1168 μg/dL),[5] while another study had seven such patients, with the highest TIBC determination being 169 μmol/L (930 μg/dL).[6] An ion exchange resin rather than the magnesium carbonate method was used in the latter study.[5] Although these reagents differ, they both serve as adsorbents for the excess iron; thus, the principle of the assays is identical. The upper limit of normal was not stated in these studies, but in our laboratory, it is 72 μmol/L (400 μg/dL). In addition to the hyperferremia of acute iron overdose, a TIBC elevation as high as 273 μmol/L (1500 μg/dL) has been observed after the therapeutic administration of iron dextran.[7] These data complement our observation (Table).

We believe we have proved our hypothesis that the increase of the TIBC in iron poisoning is a laboratory aberration because we have replicated this finding in vitro, and we have prevented its occurrence by altering the laboratory procedure (experiment 4).

Examination of the principles of TIBC determination, as picted in Fig 1, helps to provide an explanation for this ienomenon. Another source for error is that the adrbed iron is not always centrifuged out from the supertant.[8] Reliability could be improved by modifying the say or using a different one altogether. The obvious odification is to increase the amount of added magneım carbonate. However, the actual amount needed is pendent on prior knowledge of the serum iron concenıtion, and the use of variable amounts of magnesium rbonate creates a greater potential for error. Also, these terminations would then have to be consecutive rather an concurrent, which lengthens the turnaround time for est that is required on an emergent basis. A further comicating factor is that the amount of magnesium carbonate quired is also dependent on its adsorptive properties, hich can vary from one preparation to another.[4]

Total iron-binding capacity methods, based on other anytical principles, have been reported. Some used ion exange resins or hemoglobin-coated charcoal rather than agnesium carbonate,[9] while others used alumina colnns.[8] However, because the principle is the same, abormal TIBC determinations could result and indeed have en observed.[6] In one comparison study, the magnesium rbonate method was preferred.[9]

The immunochemical methods for measuring the TIBC tually measure transferrin that is then considered as the BC.[10] This is reasonable in patients with normal or nearormal iron status[10] but may not be so with the acute hyerferremia of iron overdose. In this situation, other asma constituents could contribute to the TIBC. For exnple, complexation of iron with other plasma proteins d organic ligands is known to occur in chronic hyperrremia.[11] For most laboratories, the equipment required r an immunochemical TIBC method is costly, and the chnical expertise for its determination is high.[10] Of reater importance is that its turnaround time is unsuitable r this clinical situation.

The principle that the patient with an iron overdose is t risk when the serum iron concentration exceeds the IBC is intuitively attractive. However, it ignores other efense mechanisms, such as rapid hepatic uptake of iron ith subsequent storage of ferritin. This relationship has ot been validated and has been questioned,[3] and recent linical data cast doubt on its existence.[12] The Fischer test as developed as an immediate screen for serum iron in xcess of the TIBC during an era of unavailability of rapid on and TIBC determinations,[2,6] but it was not validated ith outcome criteria.

A high TIBC, occasionally seen in iron poisoning, hould not be considered as providing a protective effect. Patient 2 (Table) in this report had chelatable iron as demonstrated by her orange urine during deferoxamine therapy despite having a serum iron concentration less than her TIBC.

Being nonautomated, the TIBC is labor intensive and prolongs the turnaround time. It can be unreliable during acute hyperferremia, and we have demonstrated that the interlaboratory reproducibility of the TIBC under conditions of normoferremia is unsatisfactory. Furthermore, the relationship between exceeding the TIBC by the serum iron concentration and clinical iron toxicity has never been shown, to our knowledge, and has been questioned.[12] Thus, we conclude that the TIBC should not be used in the decision for the initiation of deferoxamine therapy in patients with acute iron poisoning. Appropriate indications are clinical criteria, an absolute serum iron concentration, or a positive chelation challenge test.[1]

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Improving the Use of Early Follow-up Care After Emergency Department Visits

A Randomized Trial

Eliot W. Nelson, MD; Susan Van Cleve, RN, MSN, PNP; Martha K. Swartz, RN, MSN, PNP; William Kessen, PhD; Paul L. McCarthy, MD

• ***Objective:*** **To test the hypothesis that the appropriateness of parents' use of early follow-up care after emergency department (ED) visits can be improved by postvisit support from a nurse practitioner.**
Design: **Randomized controlled trial, single blinded.**
Setting: **Urban university hospital ED linked to hospital's primary care center.**
Participants: **Parents of 190 children younger than 8 years who sought care in the ED for acute illnesses and who were treated as outpatients with primary care center follow-up at the discretion of ED clinicians.**
Intervention: **Parents in the experimental group were called by a nurse practitioner who offered both individualized guidance regarding follow-up and access to a nurse practitioner for further help as needed. The control group received "usual" follow-up advice during ED visits.**
Measurements/Main Results: **In the week after the ED visits, parents in the experimental group, compared with parents in the control group, were more compliant with instructions regarding follow-up (79% vs 61%), less apt to miss appointments (15% vs 31%), and less apt to "shop" elsewhere for care (2% vs 9%). Appropriateness of follow-up was assessed in "blinded" fashion using preestablished guidelines. Inappropriate use of follow-up care was significantly reduced among experimental group subjects (10% vs 20%).**
Conclusion: **The nurse practitioner's intervention improved parents' use of follow-up care in our sample. Overall care for episodic ED users might be improved by similar interventions.**
(AJDC. **1991;145:440-444)**

Parents who bring their children to emergency departments (EDs) for acute illnesses frequently have problems with follow-up. Most EDs are poorly suited to provide continuity of care, and ED clinicians are inconsistent in providing plans for follow-up.[1] However, even when follow-up *is* available, parents often fail to make appropriate use of it.[2-6]

Inappropriate parental use of follow-up care can be most worrisome in the first days after ED visits, when the child is most likely to remain ill. "Inappropriate" use can occur in various forms, such as missed appointments, revisits to the same or another ED for nonurgent problems, failure to follow specific instructions or contingency plans, or failure to use the telephone to obtain information, test results, or further guidance. Any of these forms can raise the costs of care or adversely affect the child's health. A review of records from our hospital indicated that inappropriate follow-up occurred in 20% to 25% of cases in the week after visits to our pediatric ED for acute problems.

In this study, we conducted a randomized trial to test the effectiveness of an intervention to improve patterns of parental use of early follow-up care in an urban ED setting. We hypothesized that telephone support, given by pediatric nurse practitioners (NPs) to parents within 1 day after visits to the ED for their childrens' acute illnesses, could improve the appropriateness of the parents' use of follow-up care. Our study design allowed us to consider a variety of forms of use in the follow-up period, so that we could ascertain inappropriate overuse as well as underuse of such care.

METHODS

Setting

The study was based at the Yale-New Haven (Conn) Hospital. Patients who receive primary health care at this hospital are predominantly black or Hispanic, poor, and receiving state assistance. The Pediatric ED is open 24 hours daily for emergencies or unscheduled visits. A Primary Care Center (PCC), located across the street, provides routine scheduled medical care for patients during daytime hours on weekdays. The PCC patients who need follow-up care after ED visits are generally expected to receive this care at the PCC, which can offer better continuity of care than can the ED.

Study Design

The study protocol was approved by the Yale University Human Investigations Committee. All subjects gave oral consent to participate. The protocol permitted us not to inform participants of the randomized trial we were conducting (so as to minimize

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From the Departments of Pediatrics, Yale University School of Medicine (Drs Nelson and McCarthy), the School of Nursing (Mss Van Cleve and Swartz), and the Department of Psychology, Yale University (Dr Kessen), New Haven, Conn. Dr Nelson is now with the Division of General Pediatrics and Primary Care, University of Vermont Medical Center, Burlington. Read in part at the meeting of the Western Society for Pediatric Research, Carmel, Calif, February 9, 1989.

Reprints not available.

the "Hawthorne effect"[7]). Instead, we told subjects initially that we were conducting a survey of parent ED users, now and later over the phone, to try to learn ways of improving pediatric ED care.

Potential subjects were identified on arrival at the ED. Each child was younger than 8 years, was accompanied by a parent or usual caretaker, was free of active chronic illness, and presented with a chief complaint suggesting an acute infectious or allergic condition. Children remained eligible for the trial only if they were treated as outpatients. Further eligibility criteria required parents to be English speaking, to have access to a telephone in their home or nearby, and to identify the hospital's PCC as their chosen source for primary care for their children.

Subjects were enrolled during visits to the ED, and pretrial ("survey") data were collected uniformly. Those patients randomized to the experimental group received the telephone intervention per protocol after ED discharge, while those in the control group received usual care with respect to follow-up (see detailed descriptions below). Approximately 8 days later, outcome data were collected regarding any type or pattern of use of follow-up care over the interval, and the "appropriateness" of the use was assessed for each case.

Pretrial Baseline Data

Collection of baseline data allowed us to compare the trial groups for similarity. Methods included a standardized interview of the parent both before and after the child was seen for care, a questionnaire completed by the ED physician after ED discharge, and a review of each patient's hospital chart and ED record for the visit. We focused on factors that might influence parents' use of follow-up care, such as demographic and socioeconomic traits, previous use of health care for the child, clinical features of the ED visit, and both parents' and physicians' perceptions of the visit, including how sick the child seemed and how satisfied the parents were with the care given. When questions called for opinions or subjective assessments, either "yes/no" or Likert-format scales were used.

Trial and Intervention

Random assignment to the experimental or control group was predetermined according to study identification number with use of a random number table and a balanced block-randomization scheme. To avoid contamination of the control group and to protect the "blinded" status of the principal investigator (PI) with respect to trial-group assignment, all parents were handed a sealed envelope on leaving the ED that contained written information about the survey in which they had participated. For the experimental group parents, however, these envelopes also contained a message, saying that they would be contacted soon by telephone by an NP, and a printed yellow card, giving the names of the two NPs and a 24-hour telephone access number for reaching an NP in case of need during the child's illness.

An NP called each parent in the experimental group 6 to 18 hours after discharge from the ED. She offered further explanation about the child's diagnosis and treatment, reinforced follow-up instructions, both for specific appointments and contingency plans, and offered round-the-clock access to herself or the other NP by telephone (via the number on the yellow card) if needed. The protocol allowed her to answer questions or offer clinical assistance over the phone herself if it seemed warranted. However, she emphasized the advantages of continuity of care with the child's usual primary care provider and offered to facilitate communication with that provider if the parent wanted help.

Parents in the control group received no additional contact from the investigators until outcome interviews; thus, they received "usual care" with respect to follow-up. In usual care, plans and instructions for follow-up were at the discretion of the individual ED clinician and were communicated simply by the physician and/or nurse who discharged the child. There was no guarantee of further access to or contact with any physician or nurse already familiar with the child's case.

Outcome Data and Assessments

Prior to collection of outcome data, we developed a set of criteria for assessing the overall appropriateness of parents' use of follow-up care for their children. These preestablished criteria favored continuity and economy of care; examples of "appropriate" use included keeping appointments, following instructions regarding reuse of care, using the PCC rather than the ED for nonurgent care, and using the telephone prior to or instead of coming to the hospital for an unscheduled visit. The criteria were flexible in allowing parents to call to reschedule or cancel appointments if the need for care changed; thus, compliance with the original follow-up plan was not absolutely required for use of care to be deemed appropriate. In addition, because all subjects had identified our hospital as their choice for the child's primary care, we considered the seeking of care elsewhere ("outside care") during the follow-up period to be inappropriate.

Outcome data were collected by the PI, who remained blinded to the subject's trial group, approximately 8 days after the initial ED visit. Initially, he reviewed clinic and ED logs, both at Yale-New Haven Hospital and at the city's only other major hospital, to ascertain appointment keeping and use of care in those locations over the interval. He then telephoned each parent to conduct a standardized interview to gather detailed information on the course of the child's illness subsequent to the initial visit, the use of any follow-up care for the child, and the parents' reasons for such use.

This final interview was designed to minimize the risk of unblinding the PI regarding trial-group assignment, with questions focusing simply on how the parents felt about the child's condition and whether they had sought any care during the week. The format allowed the PI to apply the preestablished criteria directly in rating the overall appropriateness of parental use of follow-up care. The rating was then made along a four-point balanced scale (appropriate or probably appropriate vs probably inappropriate or inappropriate), giving consideration both to medical records and parents' information so that needs of individual patients were taken into account.

Validation of Outcome Assessments

To obtain an independent validation of the PI's ratings of overall appropriateness, we submitted 36 case abstracts, including many "hard-to-rate" ones, with our preestablished guidelines, to six outside "judges" experienced in urban pediatric ED care. When the ratings of these judges were pooled, agreement between their ratings and those of the PI was 94%. Agreement between individual judges' ratings and those of the PI ranged from 72% to 94%; corresponding κs were .44, .61, .67, .67, .88, and .88.

Data Analysis

Differences between trial groups with respect to both baseline variables and outcomes were evaluated principally using the χ^2 test, with Yates' continuity correction where appropriate. An α of .05 was considered significant for outcomes of the trial.

RESULTS

Characteristics of Sample: Pretrial Variables

From August 1984 to March 1985, we enrolled 190 subjects in the study. The balanced randomization scheme resulted in equal numbers of subjects initially in each trial group. Four of the subjects in the experimental group and two in the control group could not be reached for outcome interviews. Thus, the final sample available for analysis consisted of 184 subjects, 91 in the experimental group and 93 in the control group.

Some of the key demographic characteristics of the 184 subjects and clinical features of their initial ED visits are shown in Tables 1 and 2. The trial groups were highly similar in these characteristics and most others assessed at baseline. However, as shown, the groups did differ with respect to a few of the important baseline variables, including parents' educational level, the degree of fever in the children, the recorded primary diagnoses for the children, and the specific forms of treatment prescribed. (Although these differences may have arisen by chance considering the multiple comparisons involved, we did stratify the sample with respect to each of these variables

Table 1.—Demographic Characteristics of Sample (n=184)

Characteristic	%
Children (median age, 27 mo)	
Gender, % M	48
Race, % black	77
Parents	
Single	86
Education, % completed 12th grade	62*
Unemployed	74
Receiving state assistance	80

*Experimental vs control, 54% vs 71%, respectively ($P<.05$).

Table 2.—Clinical Features of Emergency Department Visits (n=184)

Feature	%
Chief complaints	
Fever	47
Respiratory/earache	23
Vomiting or diarrhea	7
Rash	13
Other	10
Recorded temperature, °C	
<38	55
38 to <39	17
39 or higher	21*
Not measured	7
Laboratory tests done, % of patients	33
Recorded primary diagnoses	
Viral infection	45
Bacterial infection/otitis	37†
Candida or unspecified rash	11
Other	7
Primary treatment prescribed	
None or supportive only	22
Antibiotic	46‡
Drug(s) other than antibiotics	32

*Experimental vs control, 14% vs 27%, respectively ($P<.05$).
†Experimental vs control, 51% vs 25%, respectively ($P<.001$).
‡Experimental vs control, 57% vs 35%, respectively ($P<.01$).

Table 3.—Plans for Use of Follow-up Care During Week After Emergency Department Visit

Type of Plan	Proportion of Subjects, % (n=184)
None	17
Contingency ("prn") only*	42
Definite appointment	20
Other definite instructions	12
More than one type of definite plan	7
Other/unclear	2

*prn indicates as occasion requires.

look for any impact on the trial. Importantly, this strat- ication revealed that the differences did not affect the tcome of the trial.)

With regard to previous use of care for the child, al- ough 89% of the parents had already sought well-child re in the PCC (and more than 90% of these expressed tisfaction with that care), only 15% had sought care for episode of acute illness in the child at the PCC. By con- st, 77% of the parents had previously sought care in the for acute illness in the child, including 28% who had sought such care at least twice in the preceding 6 months. Thus, the sample reflected a clear previous parental predilection for ED use for illness in their children.

Table 3 shows the types of follow-up plans established by the ED clinicians for further care within the first week after the visit. The majority of patients were not believed to require any definite short-term use of follow-up care, although many were given contingency instructions (eg, to call the physician if the child's condition worsened). Definite appointments and/or instructions regarding the use of follow-up care (eg, absolutely to call the physician for test results or to discuss the need for further care) were given in 39% of the cases. There were no significant differences between the trial groups with regard to follow-up plans.

Parents and physicians independently rated the seriousness of the childrens' sicknesses along a five-point scale (dangerously, very, moderately, mildly, or hardly sick). Parents rated their children as moderately, very, or dangerously sick in 57% of cases, whereas physicians rated only 17% of the children as moderately sick or sicker. Perhaps accordingly, physicians classified a majority (56%) of these initial ED visits as inappropriate. Parents generally expressed satisfaction with the visits (48% "highly" and 43% "somewhat" satisfied), as well as with the instructions given them (84% felt these were "very clear").

The Intervention and Outcomes of the Trial

The NP's intervention consisted of only a single telephone call in 78 (86%) of the experimental group cases. For the majority of these calls, the total time required of the NP was less than 5 minutes. The total time spent by NPs in phone contact with parents exceeded 15 minutes for only 8% of these parents, and only five of the parents made use of the NP's availability by phone. The NPs were unable ever to reach three of the parents by phone. These parents were nevertheless considered in the experimental group for analysis because they had received the initial part of the intervention.

During the first week after the initial ED visit, the majority of subjects in this study made no use of follow-up care. In most of these cases, it was not necessary because the child's illness improved or resolved and no specific appointment or instructions for further care had been given. In such cases, the "use of follow-up care" was assessed as appropriate. Similarly, among the 71 patients for whom definite plans for follow-up had been established for the 1-week interval, most parents appropriately kept appointments and/or followed specific instructions.

However, several types of use of follow-up care occurred that were assessed as inappropriate, and in this respect the trial groups showed differences (Table 4). Parents in the experimental group who were given definite appointments and/or instructions for follow-up were much more likely to comply with these than were parents in the control group. Moreover, parents in the experimental group were much less likely to make use of outside care. Unnecessary revisits to the ED were unusual, but they occurred with equal frequency in the two groups. (It should be noted that more than one type of inappropriate use occurred in some cases.)

The ratings of overall use of follow-up care for each patient showed that inappropriate or probably inappropriate use occurred with significantly greater frequency in the control group than in the experimental group (20.4% vs

Table 4.—Results of Trial

ypes of Inappropriate Use of Follow-up Care	Frequency Within Groups (%)	
	Experimental	Control
issed appointments (among those given appointments)	3/20 (15)	8/26 (31)
ailure to follow instructions (among those given them)	3/14 (21)	7/18 (39)
se of outside care (among all subjects)	2/91 (2)	8/93 (9)
nnecessary revisits to emergency department (among all subjects)	2/91 (2)	2/93 (2)

% [Table 5]). Thus, the NP's intervention reduced the uency of such inappropriate use of follow-up care by t.

inally, we performed exploratory analyses to find those groups, identified at baseline, that were most respon- e to the intervention. Inappropriate use of follow-up e was most significantly reduced for experimental up subjects, compared with controls, within three sub- ups as follows: parents whose children were younger n 18 months (n = 69; 3% vs 29%, $P<.01$); subjects with ther parent employed (n = 136; 7% vs 24%, $P<.01$); and ents who perceived their children as at least "moder- ly" sick at the initial visit (n = 105; 6% vs 24%, $P<.02$). ause these analyses required multiple comparisons,[8] can only consider their results as suggestive.

COMMENT

rovision of follow-up care, including a return of pa- nts to their primary care delivery system, is an impor- t aspect of ED care[9] that frequently fails to receive suf- ient attention, perhaps because ED physicians are often nfronted with patients who fail to comply with low-up arrangements. Lack of good follow-up contrib- es to the inappropriateness of episodic ED use, which turn is associated with high rates of hospitalization, h costs of care, and poor continuity of care.[10-12]

Weitzman et al[5] observed in 1980 that follow-up care for ildren after ED or "urgent-care" clinic visits had not been ll-studied. Past efforts to improve follow-up and overall e of care among such children have included mailed minders,[13] telephone reminders,[6] and increased avail- ility of comprehensive and continuous care.[11] The in- rventions studied have not provided individualized or ecific support to parents, and the studies have generally cused on long-term use[12,14] and/or on appointment keep- g as the sole outcome. To our knowledge, no previous udy has examined all forms of parental reutilization of re (instead of only appointment keeping) within specific isodes of illness, even though authors have suggested at such reutilization should be especially amenable to fluence.[15]

The design of our intervention was based in part on the ork of Korsch et al,[16] who showed that both improved mpliance and increased parent satisfaction were asso- ated with better physician-parent communication in an rban hospital outpatient and ED setting. Because many D visits are considered inappropriate by physicians[17] (a nding replicated by our study), we believed that discus- ion of follow-up plans might often be relatively neglected.

Table 5.—Results of Trial

Ratings of Overall Appropriateness of Use of Follow-up Care	Frequency (%) of Ratings Within Trial Groups*	
	Experimental	Control
Appropriate or probably appropriate	82/91 (90.1)	74/93 (79.6)
Inappropriate or probably inappropriate	9/91 (9.9)	19/93 (20.4)

*$\chi^2 = 3.96$; $P<.05$.

We thus hoped that even a modest amount of additional supportive communication would improve patterns of follow-up.

Within the early follow-up period on which we focused, our intervention was successful in improving parents' reuse of care. Specifically, it increased short-term compliance with both appointments and instructions, and it also reduced the frequency of "shopping" elsewhere for care for the same problem.

Our results complement and extend the findings of Korsch et al[16] by showing that an intervention consisting of increased supportive communication can improve parental use of health care in a similar setting. On the other hand, the fact that inappropriate use of follow-up care occurred among almost 10% of our experimental group subjects underscores the challenge facing any such effort.

The clinical significance of the improvements in follow-up that we observed may have been relatively minor in some of these cases, but the *potential* importance for individual cases was illustrated vividly by the experience of one noncompliant subject (from the control group) in our study:

> A 22-month-old girl had a 3-day history of fever, cold, and vomiting. The mother reported she had been playful at home. In the ED her rectal temperature was 40.5°C, and examination revealed no focal source of infection. A blood sample was taken for culture. A diagnosis of "probable viral syndrome" was made; treatment included acetaminophen and a decongestant. A follow-up appointment for the next day with the child's physician at the PCC was arranged; the mother was also told to return sooner if the child's condition worsened.
>
> The mother failed to appear for the PCC appointment. However, a day later she brought the child back to the ED; the child was then found to have pneumonia with a pleural effusion and was admitted to the hospital.

Although our experience with seriously ill febrile children was not extensive enough in this study to allow statistically significant conclusions, our results suggest that an intervention such as ours will increase the likelihood of appropriate follow-up for some of these most worrisome patients and might in turn decrease morbidity for some of them.

A major cause of inappropriate follow-up may be that parents do not clearly understand options for care or feel that they have access to appropriate forms of care. The NPs in our study were able to offer guidance, using clinical judgment and their training[18] where necessary, to help parents make appropriate decisions. The study design allowed us to examine the intervention of extra supportive communication in a controlled fashion *apart* from usual care; we recognize that other clinicians, including physicians themselves, might provide equally effective extra support. While a "follow-up clerk" or secretary has sufficed in projects designed simply to increase appointment keeping,[6,19] such an individual might lack clinical skills needed to help parents with unforeseen questions regarding follow-up.

It is difficult to predict financial costs and benefits of such an intervention based on a trial of our size. However, our intervention required little time and only a single call in most cases; and we would expect that a 50% reduction in inappropriate use of follow-up care would improve cost-effectiveness as well as quality of care. Moreover, our exploratory analyses suggest that similar interventions might be aimed more efficiently at certain "target" parents most likely to respond (eg, those who are unemployed or whose children are younger than 18 months).

Lack of existing criteria for evaluating appropriateness of follow-up made it necessary for us to develop our own criteria. It was striking that the ratings of the outside judges, who considered many of the most difficult-to-rate cases, showed substantial agreement with those of the PI. This suggests that similar criteria might be useful in other settings or in efforts to evaluate the quality of follow-up care.

In summary, we have shown that a supportive telephone call, made to parents within a day of visits to our ED for their childrens' acute illnesses, improved use of follow-up care for those illnesses. We believe that interventions such as this one can improve the overall provision of health care to poor urban children whose parents frequently seek attention for acute illnesses in EDs. Such efforts must continue to emphasize the importance of supportive communication and access to continuity of care. We believe they can be performed efficiently and can po-entially decrease costs by decreasing overuse of unnecessary care. For disadvantaged children whose parents might have related poorly to health care systems in the past, such direct interventions may be the most effective way of influencing parental behavior to achieve improved use of care in the future.

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Influenza Vaccination in the Prevention of Acute Otitis Media in Children

Terho Heikkinen, MD; Olli Ruuskanen, MD; Matti Waris, MSc; Thedi Ziegler, PhD;
Mikko Arola, MD; Pekka Halonen, MD

• We studied a new approach to the prevention of acute otitis media through the administration of influenza vaccine to 187 day-care center children aged 1 to 3 years before the influenza A epidemic of 1988-1989. The control group consisted of 187 unvaccinated children of similar age and background. During the 6-week study period, influenza A infection was diagnosed in five (3%) of 187 vaccinees and in 29 (16%) of 187 controls. Acute otitis media developed in three (60%) of five vaccinees with an influenza A infection compared with 18 (67%) of 27 controls (excluded were two children with a double viral infection). The incidence of acute otitis media associated with influenza A was reduced by 83% in the vaccinees. The total number of children with acute otitis media in the vaccine group was 35, compared with 55 in the control group, disclosing a 36% reduction among the vaccinees. We conclude that influenza vaccination decreases the incidence of acute otitis media in children during an influenza A epidemic, suggesting also that other vaccines against respiratory viruses may be an effective way to reduce the incidence of acute otitis media.

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Otitis media in children is a major health care problem, not only because of the distress it causes to the child and his or her family but also because of the substantial economic burden to the health care system.[1] According to Teele et al,[2] more than 60% of children in the United States have had at least one attack of acute otitis media (AOM) by their first birthday and more than 80% have had an attack by 3 years of age. Similar findings have been reported in Finland.[3] Obviously, it is of utmost importance to find a way to prevent otitis media in children. In most cases, AOM is a bacterial infection. A great deal of research has been conducted in an attempt to develop a bacterial vaccine for otitis media.[4] The results of extensive vaccine trials against the most common causative agent, *Streptococcus pneumoniae*, have not so far been very satisfying.[5-8]

Clinical evidence has shown that in most cases AOM is preceded by a respiratory viral infection.[9] A simultaneous viral infection has been documented in 26% to 42% of patients with AOM.[10-14] The greatest risk for the development of AOM lies in infections caused by respiratory syncytial viruses (RSVs), rhinoviruses, influenza A viruses, or adenoviruses.[11,14,15]

Our study was based on the hypothesis that prevention of the preceding respiratory viral infection would decrease the incidence of AOM. We decided to concentrate on the influenza A virus infection because an available vaccine has been shown to be safe and effective, even in young children,[16] and also because AOM is a common complication of influenza A infection.[15] The attack rate for influenza in children is, moreover, usually high (30% to 60%),[17] epidemics are of short duration, and there is a rapid and sensitive immunoassay available for the direct detection of influenza virus antigens in nasopharyngeal aspirates.[18]

SUBJECTS AND METHODS

Subjects

In October 1988, of a total of 26 day-care centers serving 831 healthy children in Turku, Finland, all 291 children from 11 randomly selected day-care centers were invited to be vaccinated against influenza; the enrollment of children known to be allergic to eggs was discouraged. Informed consent was obtained from the parents of 207 children (71%); 14 children were vaccinated only once or not at all because of either acute infection or absence from day care at the time of vaccination. A total of 193 children (66% of the original total; range, 33% to 83% per center) were vaccinated twice, as recommended. Six children were excluded from the analysis because they left day care before the study began. The final vaccine group consisted of 187 children.

An unvaccinated control group was formed by inviting all 273 children from eight other randomly selected day-care centers in Turku to participate. Informed consent was obtained from the parents of 188 children (69% of the total; range, 56% to 82% per center). One child was excluded from the analysis because of absence from day care during the study period. The final number of children in the control group was 187.

Data on the families and children's previous infections were assembled from a questionnaire completed by the parents (Table 1). The mean age of the children was 2.2 years in both groups. Most of the children were otitis prone: 128 (68%) of 187 children in the vaccine group and 118 (63%) of 187 children in the control group had a history of at least two attacks of AOM. The average number of previous attacks of AOM in the vaccine group was 4.5 (range, 0 through 30) compared with 4.2 (range, 0 to 25) in the control group. No significant differences were noted between the groups regarding the number of siblings, smoking in the household, or earlier adenoidectomy or placement of tympanostomy tubes.

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From the Department of Pediatrics (Drs Heikkinen, Ruuskanen, and Arola) and Virology (Drs Ziegler and Halonen and Mr Waris), University of Turku (Finland).

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Reprint requests to the Department of Pediatrics, Turku University Hospital, SF-20520 Turku, Finland (Dr Heikkinen).

Table 1.—Characteristics of the Study Groups*

Variable	Vaccinees	Controls
Total No. of children	187	187
Male (%)	92 (49)	103 (55)
Mean age, y (range)	2.2 (0.9-3.5)	2.2 (0.6-4.2)
<1	1	5
1-<2	76	65
2-<3	67	76
≥3	43	41
No. of siblings (range)	0.6 (0-3)	0.6 (0-3)
Smoking in the household (%)	30 (16)	42 (22)
No. of previous attacks of AOM (range)	4.5 (0-30)	4.2 (0-25)
No. of children with ≥2 episodes of AOM (%)	128 (68)	118 (63)
Adenoidectomy (%)	40 (21)	47 (25)
Tympanostomy tubes (%)	35 (19)	35 (19)

*AOM indicates acute otitis media.

The study protocol was approved by the Ethical Committee of Turku University Hospital.

Vaccination

The vaccinations were administered between November 17 and December 15, 1988, with a trivalent subvirion influenza virus vaccine (Fluzone, Connaught Laboratories Inc, Swiftwater, Pa) containing the three prototype strains recommended for the season (influenza A/Taiwan/1/86[H1N1], influenza A/Sichuan/2/87[H3N2], and influenza B/Victoria/2/87). Two doses of 0.25 mL were injected into the deltoid muscle, with a 3-week interval between the injections. No serious adverse reactions were reported.

Study Period

From the beginning of November 1988, an intensive screening of influenza virus activity in the community was conducted, with the use of rapid viral antigen detection in nasopharyngeal aspirates of febrile children seen both in private practice and at the University Hospital in Turku. Before commencement of the study, 340 specimens were tested.

The first case of influenza A to be diagnosed in Turku was found on December 2, 1988. The study commenced on December 19, after 11 influenza A infections had been diagnosed in children in the city, and it was discontinued on January 26, 1989, at 1 week after the last recorded case of influenza A in the study population. The first case of influenza A among the children enrolled in this study was diagnosed on December 19. During the epidemic, both H1N1 and H3N2 strains of influenza were circulating, the latter being predominant in Turku.

During the 6-week study period, the parents of all 374 children were asked to bring their children to the study office whenever fever or signs of a respiratory tract infection appeared. No charge was made for these visits. The parents were not asked by the study physicians (T.H., M.A., and O.R.) whether the child had been vaccinated, which means that in most cases the investigator did not know to which group the child belonged. During each episode of infection, a nasopharyngeal mucus specimen was aspirated for rapid viral antigen detection. In 14 cases, however, it proved impossible to obtain the specimen (seven cases in each group). Children without AOM at the first examination were reexamined 1 week later, unless symptoms of AOM developed in the meantime. The diagnosis of AOM was based on signs and symptoms of acute infection, together with the presence of middle-ear fluid detected by pneumatic otoscopy or purulent discharge from a tympanostomy tube.

Table 2.—Results of Viral Antigen Detection in Nasopharyngeal Aspirates and the Corresponding Numbers of Cases With AOM in the Study Groups*

	Vaccinees (n=187)		Controls (n=187)	
Virus	No.	AOM	No.	AOM
Influenza A	5	3	27	18
Influenza A and adenovirus	0	0	1	1
Influenza A and RSV	0	0	1	0
RSV	1	1	9	5
Adenovirus	5	2	4	1
Parainfluenza type 3	7	5	0	0
Parainfluenza type 1	1	0	0	0
Virus detected	19	11	42	25
No virus detected	79	25	65	31
No specimen available	7	0	7	4
Total No. of respiratory tract infections or episodes of AOM	105	36	114	60

*AOM indicates acute otitis media; RSV, respiratory syncytial virus.

Viral Diagnosis

Nasopharyngeal secretions were aspirated through the nostrils with use of a disposable mucus extractor (Vygon, Laboratoires Pharmaceutiques, Ecouen, France). The specimens were transported at room temperature to the laboratory, where they were processed the following day. Viral antigens in the aspirates were detected by one-incubation, monoclonal time-resolved fluoroimmunoassay for influenza A and B viruses; parainfluenza types 1, 2 and 3 viruses; RSV; and the group-reacting hexon antigen of adenoviruses.[19-22] The reliability of time-resolved fluoroimmunoassay with the use of monoclonal antibodies for the detection of influenza virus antigens has been established.[18]

Statistical Analysis

Significance testing was performed by means of the standard χ^2 test. Confidence intervals were calculated at the 95% level of confidence.

RESULTS

During the study period, 105 respiratory tract infections were recorded in the 187 vaccinees, compared with 114 in the 187 controls; in each group, 14 children each had two episodes of infection. Acute otitis media was diagnosed in 36 (34%) of the 105 cases in the vaccine group, compared with 60 (53%) of the 114 children in the control group. One child in the vaccine group and five in the control group had two consecutive attacks of AOM, the numbers of children with AOM during the study thus being 35 and 55, respectively ($P<.02$).

A total of 205 nasopharyngeal aspirates were obtained from the children, with viral antigen being detected in 61 cases (30%). Viral findings and the corresponding numbers of cases of AOM are presented in Table 2. Influenza A was diagnosed in five (3%) of the 187 vaccinees (confidence interval, 1% to 5%), three (60%) of whom also had AOM. In the control group, influenza A was diagnosed in 29 (16%) of the 187 children (confidence interval, 11% to 21%; relative risk, 5.8; $P<.0001$). The protective efficacy of the vaccination against influenza A was 83% (five vs 29). Two controls had both influenza A and another viral infection simultaneously, one with adenovirus and the other

h RSV. Not including these two children, AOM de-
ped in 18 (67%) of 27 controls with influenza A. The
rease in the incidence of AOM associated with influ-
a A in the vaccine group was 83% (three vs 18; $P<.001$).
nfluenza A was detected in the participants of four (of
day-care centers in the vaccine group compared with
(of eight) day-care centers in the control group. Other
ses detected in the children studied were adenovirus,
V, and parainfluenza types 1 and 3 viruses.

COMMENT

Ve studied a new approach to the prevention of AOM
ough prevention of the respiratory viral infection that
ally precedes it. The results of our study suggest that
may be a successful way to prevent AOM when an
ctive vaccine against a specific predisposing virus is
ilable. In our study, the efficacy of the vaccination
inst influenza A was 83%, with a consequent 83% de-
ase in the incidence of AOM associated with influenza
nfection in the vaccinees. Obviously, the most impor-
t result of our study is, however, the clear-cut 36% re-
ction in the overall morbidity due to AOM in the vaccine
up, although the attack rate for influenza A in the con-
l group was only 16% and several other respiratory vi-
es were present in the community.

treptococcus pneumoniae is the most common causative
ent in AOM, and several pneumococcal vaccine trials to
vent AOM have been reported.[5-8] Immunization with
polyvalent pneumococcal polysaccharide vaccine re-
ces the number of episodes of AOM caused by the se-
ypes contained in the vaccine when there is a good an-
ody response in the children. The immunogenicity of
me of the serotypes commonly associated with AOM,
wever, is poor, especially in children younger than 2
ars, and the trials have therefore failed to show any con-
cing reduction in the total number of cases of AOM.
e conjugated pneumococcal vaccines that have recently
en developed may prove more effective in the preven-
n of AOM in young children.[23]

Our findings are in accordance with earlier evidence of
lear connection between respiratory viral infections and
M.[11,15,24] In a 14-year longitudinal study, Henderson et
[1] showed that respiratory viral infections conferred a
eater risk of AOM than did colonization of the nasophar-
x with *S pneumoniae*. Not all respiratory viruses predis-
se equally to AOM, but it appears that the principal
lprits are RSV, rhinovirus, influenza A virus, and ad-
ovirus.[11,14,15] In particular, influenza A and RSV cause
ajor epidemics. If children could be protected from these
ruses, there would be a considerable decrease in the in-
dence of AOM. A fusion-protein vaccine against RSV has
cently been developed, and this has been shown to be
fe in toddlers.[25] Further clinical trials will be needed to
termine its efficacy in the prevention of RSV infection
d RSV-associated otitis media.

Acute otitis media was diagnosed in 67% of the unvac-
nated children who had an influenza A virus infection.
an earlier study of hospitalized children with influenza
, 35% appeared to have AOM.[15] The difference can most
robably be explained by the fact that our study concerned
ildren from day-care centers, most of whom were otitis
rone and also younger than those studied earlier.

Influenza vaccination is currently recommended for
igh-risk children and those in close contact with them,
lthough other children (for example, those in day care)
re also thought to benefit from the vaccination.[26] Because
hildren at school and in day-care centers are the main
isseminators of viruses during epidemics, there has been discussion as to whether all children should be regularly vaccinated against influenza.[17] To achieve this, however, would not be easy. First, it is necessary to administer the vaccine annually, and two doses must be given in the first instance. Then, there is the question of the continual antigenic variation of influenza viruses and the resulting fluctuation in the efficacy of the vaccine. Our findings nevertheless support the view that children in day care, especially those suffering from recurrent otitis media, would greatly benefit from influenza vaccination. As an alternative to vaccination, the antiviral agent rimantadine hydrochloride could be used to prevent influenza A infection.[27]

Ours was not a double-blind, placebo-controlled study, but this was largely offset by the fact that the parents were not asked whether their child had been vaccinated. In most cases, therefore, the investigator did not know to which group the child belonged; nor were the viral results available when AOM was diagnosed. There was, nevertheless, a similar incidence of AOM in children with different respiratory virus infections in the two groups. It could be argued that because the assignment of children to the groups was based on randomization of the day-care centers, not individual children, a possible clustering of influenza A around a limited number of day-care centers might invalidate the study. Influenza A was diagnosed in participating children from four of 11 day-care centers in the vaccine group compared with six of eight day-care centers in the control group. The smaller incidence of influenza in the vaccinees (3%) compared with the controls (16%) is most likely a result of the protective effect of the vaccine, but lesser exposure to influenza A virus is also possible. It must be emphasized, however, that the actual exposure to influenza A in both groups was in all probability greater than recorded, because about one third of children in each day-care center were not enrolled in the study; consequently, their possible morbidity due to influenza could not be demonstrated.

In conclusion, our findings suggest that influenza vaccination considerably decreases the incidence of AOM in children during an epidemic of influenza A. It therefore seems possible that other vaccines against respiratory viruses may also be an effective way to reduce the incidence of AOM.

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The Pediatric Program Director

An Analysis of the Role and Its Problems

Jeffrey C. Weiss, MD; Robert A. Doughty, MD; Richard Lampe, MD

• A questionnaire designed to elicit information about the work environment, knowledge, and stresses of pediatric residency program directors was mailed to the 235 member programs of the Association of Pediatric Program Directors (APPD). At the time that the 187 respondents (80% return rate) assumed responsibility for their training programs, many rated their knowledge of various aspects of residency program administration as "poor." The respondents indicated that a lack of time, the pressures of too many other academic responsibilities, and a fear of not "filling" all positions in the National Intern Matching Program created much personal stress. Most program directors felt that educational conferences designed to teach educational methods, and administrative skills, and provide technical information knowledge necessary for residency program supervision would be beneficial.

(*AJDC*. 1991;145:449-452)

In April 1989, a workshop entitled "Stress and Burnout in Residency Program Directors" was held as part of the Sixth Annual Pediatric Chief Residents and Program Directors Conference at the Alfred I. duPont Institute in Wilmington, Del. The participants identified and discussed numerous problems related to fulfilling the role of a residency training program supervisor. As an outgrowth of the workshop, the present study was designed to collect demographic information about those pediatricians serving as program directors, to identify areas that program directors believed created major job stress, and to determine the skills or areas of learning in which the directors believed they had been inadequately prepared by their educational experience.

METHODS

A 75-item, four-page questionnaire was mailed to the 245 member programs of the APPD. Ten programs were identified as having closed or merged. Of the remaining 235 programs, 187 (80%) returned the completed form.

The questionnaire contained items designed to elicit information about the individuals who were program directors and about their experience, job description, time allotments, budget, and support staff. For 12 job-related areas, the program directors were asked to respond to the question, "How would you rate your knowledge (excellent, good, fair or poor) at the time you initially became program director?" The directors were also asked to indicate on a five-point Likert scale, "How much personal aggravation and stress does each of the following [23] items create for you?" The questionnaire stated specifically, "We want to know what bothers you the most, not necessarily what takes up most of your time!"

A high score of "4" or "5" indicated that the item represented a major problem and created a good deal of stress for the program director. Low numbers signified that the item was not a problem. Finally, the respondents were asked to indicate whether they believed an extended educational conference for program directors would be of value, and, if so, which of three topic areas (basic educational methods, administrative skills, or technical information for program directors) would be most beneficial. All responses were statistically analyzed using a microcomputer (Apple Macintosh SE, Apple Computer, Cupertino, Calif) and statistical software (Statview, Brainpower Inc, Calabasas, Calif).

RESULTS

Program Director Demographic Data

The sample consisted of 145 men (78%) and 37 women (20%); five anonymous program directors did not indicate their gender. The respondents' mean (±SD) age was 48±8.8 years, with an observed age range of 32 to 68 years (Table 1). Fifty-one percent of the respondents had achieved the rank of professor, 26% were associate professors, and 22% were assistant professors. Thirty-nine percent functioned as department chairperson as well as program director. Table 2 shows the distribution of specialty training among program directors. The number of

Department Editors.—*Hugh D. Allen, MD, Columbus, Ohio; Fredric Burg, MD, Philadelphia, Pa; Harold Levine, MPA, Galveston, Tex; Barbara Starfield, MD, Baltimore, Md; Larrie W. Greenberg, MD, Washington, DC.*

Purpose.—*This department is intended to share information concerning educational efforts in the broad field of pediatrics. We welcome studies on the following topics: undergraduate and graduate education in medicine and allied health occupations; continuing education of health professionals; education of patients and families; and health education for the general public, the community, and organizations that contribute to the promotion and improvement of the health of children.*

Editorial Comment.—*Did you feel that your residency training program director was well prepared and had adequate time for the task? If you said yes, this survey indicates that many directors feel differently. See what you think about the suggestions for improvement.*—H.D.A.

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From the Departments of Pediatrics, Jefferson Medical College, Philadelphia, Pa (Dr Weiss); Alfred I. duPont Institute, Wilmington, Del (Dr Doughty); Walter Reed Army Hospital, Washington, DC (Dr Lampe); and the Association of Pediatric Program Directors.

Reprint requests to the Department of Pediatrics, Jefferson Medical College, 1025 Walnut St, Philadelphia, PA 19107 (Dr Weiss).

Table 1.—Age Distribution of Program Directors

Age, y	No. (%) of Directors (n=176)*
25-34	10 (6)
35-44	54 (31)
45-54	71 (40)
55-64	34 (19)
≥65	7 (4)

*Eleven directors did not answer this question.

Table 2.—Distribution of Specialty Training

Specialty	No. (%) of Directors
General pediatrics	60 (32)
Neonatology	27 (14)
Infectious disease	22 (12)
Endocrinology	14 (7)
Nephrology	12 (6)
Hematology	12 (6)
Cardiology	10 (5)
Other (miscellaneous)	30 (16)

years that the program director had served to date is shown in Table 3, along with information about job longevity of the program's prior director. These data clearly demonstrate the rapid turnover in the position of residency program director. Those program directors who were not departmental chairpersons served for significantly shorter periods than those who were also departmental chairpersons (5.4 years vs 9.3 years; $t=3.77$; $P=.0002$).

Working Situation of Program Directors

Only 28% of the respondents indicated that they had any type of formal job description and only 13% had been allotted a specific number of hours or percentage of time to accomplish their duties as program director. Fifty-one percent had a formal budget for the residency program, but the chairperson was in control of the budget in 60% of the programs with nonchairperson directors. On average, the program directors devoted 27% of their time to residency administrative activities, 21% to other administrative activities, 23% to direct patient care, 22% to teaching, and only 7% to research activities. Table 4 shows the percentage of directors who had the help of various support staff in the operation of their residency programs. In response to the question, "When you were appointed program director, did you receive a significant raise or increase in fringe benefits?" 73% of the directors answered "No."

Initial Knowledge Needed for Job Performance

Table 5 shows, for each of 12 content areas, how the respondents rated their knowledge at the time they assumed the role of program director. A large percentage of the program directors indicated weak initial knowledge in almost all of the educational, technical, and administrative aspects of their job.

Table 3.—Program Director Job Longevity*

No. of Years as Program Director	No. (%) of Respondents (n=186)	No. (%) of Predecessors (n=148)
≤3	69 (37)	54 (36)
4-6	49 (26)	45 (30)
7-9	21 (11)	14 (9)
≥10	47 (25)	35 (24)

*The numbers do not total 187 because one director did not indicate his job longevity and 39 were either directing new programs or were unaware of their predecessor's job longevity.

Table 4.—Support Staff

Position	No. of Support Staff (% of Directors)
Secretary	167 (89)
Administrative assistant	56 (30)
Education specialist (PhD)	21 (11)
Associate director (MD)	72 (39)
Chief resident (postgraduate level 4)	63 (34)

Table 5.—Knowledge Level On Becoming Program Director*

	Knowledge Level, No. (%) of Directors			
Knowledge Area	Poor	Fair	Good	Excellent
Curriculum design	22 (12)	56 (30)	85 (46)	22 (12)
Evaluation methods	19 (10)	72 (39)	72 (39)	23 (12)
"Match" process	13 (7)	51 (28)	77 (42)	42 (23)
Recruiting methods	20 (11)	62 (33)	80 (43)	24 (13)
RRC requirements	33 (18)	66 (36)	60 (33)	24 (13)
Board certification	16 (9)	44 (24)	86 (46)	39 (21)
Resident stress issues	14 (8)	56 (30)	96 (51)	19 (10)
Dealing with difficult and impaired residents	30 (16)	69 (37)	70 (38)	17 (9)
Conflict resolution	21 (11)	56 (30)	87 (47)	22 (12)
Fiscal issues/budgets	58 (31)	56 (30)	54 (29)	18 (10)
Maternity leave policies	53 (29)	62 (34)	62 (34)	8 (4)
Time management	24 (13)	67 (36)	73 (39)	21 (11)

*RRC indicates Residency Review Committee. The numbers in each knowledge area do not all total 187 because some directors did not answer each question.

Problems Faced by Program Directors

Table 6 indicates the amount of stress that each of 23 tasks or problems reportedly caused for program directors. The first column shows the mean Likert scale scores and the second column indicates the percentage of directors who gave the item a score of "4" or "5," indicating that the item was a major problem for them. No strong correlations were found when the scores on these items were analyzed with respect to program director age, gender, or job longevity.

Table 6.—Problems for Program Directors

Problem Area*	Mean Likert Scale Score	Major Problem (Score of 4 or 5), % of Directors
Lack of time	3.49	56
Too many other practice or academic responsibilities	3.40	52
Fear of not "filling" in the match	3.38	52
Completing questionnaires	3.32	44
Recruiting and interviewing	3.15	40
Counseling residents with problems	3.11	41
ACGME accreditation	3.11	39
Rescheduling (eg, illness, pregnancy)	3.09	41
Resident working-hour limitations	3.02	37
RRC requirement changes	3.02	35
Lack of adequate support staff	3.01	37
Dealing with hospital administration	2.97	33
Lack of time allotted for program administration	2.85	35
Being a buffer for resident-faculty conflict	2.83	29
Curriculum (need for improvement)	2.74	27
Lack of budget or financial control	2.73	26
Scheduling (eg, block, night)	2.72	30
National funding policies for Graduate Medical Education	2.72	28
Evaluating residents and giving feedback	2.72	24
Lack of clarity of responsibilities	2.38	21
Lack of faculty support	2.29	19
Patient complaints about residents	1.89	5
Lack of chairperson support	1.62	9

*ACGME indicates the Accreditation Council on Graduate Medical ucation; and RRC, Residency Review Committee.

Attitudes About an Extended Conference for Program Directors

Eighty-six percent of the directors said that an educa- onal conference to teach them the skills and provide the formation needed to be an effective program director ould have been valuable when they assumed their jobs. eventy-five percent indicated that they would still find ich a conference useful and almost all (88%) in that group ere willing to attend a seminar lasting at least 2 days. orty-five percent of all directors chose basic educational ethods as their first choice of topics for this proposed minar; examples of methods included curriculum de- gn, formulation of learning objectives, evaluation and edback methods, and methods to improve conferences. irty-six percent wanted to develop administrative skills, ich as directing the budgetary process, leadership and otivational techniques, conflict management, and meth- ds to deal with problem residents. The primary choice of % of the program directors was technical information, which included the residency program accreditation process, Residency Review Committee requirements, the certification process of the American Board of Pediatrics, and technical aspects of the National Intern Matching Program.

COMMENT

The job of a residency program director is complex and requires special knowledge and skills. The director is expected to be teacher, evaluator, employer, career counselor, scheduler, advisor, arbitrator, and administrator. He or she must have a working knowledge of the laws, rules, and regulations of the many agencies that are responsible for the accreditation of training programs and the licensing and certification of physicians. The program director is responsible for obtaining highly competent trainees for the program, providing them with a good curriculum, measuring and providing feedback about their progress, and identifying and dealing with those trainees who are impaired or otherwise having difficulty.

When dismissal of a resident is being considered, the program director must follow "due process" requirements so that legal action against the program can be avoided. The director is often called on to help create and revise schedules, to ensure that residents are providing competent medical care, to arbitrate disputes between faculty members and residents, to eliminate stress, and to "keep everyone happy." The program director in an academic center must also meet committee responsibilities, write scientific papers and grants, teach medical students, and provide direct patient care. He or she must also write letters of recommendation, sign loan deferment forms, and fill out questionnaires. This diversity of roles must be accomplished within an environment of limited resources, time constraints, and little formal training.

For decades, industry has invested significant resources to train middle and senior management staff and to promote their personal growth and retention. It is only in recent years that the managerial role of physicians has gained attention. The American College of Physician Executives, established in 1989, serves as a forum for research, training, and group discussion relating to skills applicable to physicians in senior management roles.[1] Several medical specialties sponsor periodic orientation and training events for new chairpersons. Management skill training activities for chief residents have recently emerged.[2] To date, however, little attention has been paid to developing effective management skills in the critical "middle manager" role of residency program director.

The issue of stress during residency training has received much attention in recent years. Among the many stressors that have been identified by house officers are a lack of faculty support, a poor learning environment, and an insufficient number of good role models.[3-6] It is not easy for a program director to provide support to others and to create a good learning environment if he or she feels time pressures. As Pfifferling[7] pointed out, "harried, overworked, time-juggling attendings" are not particularly good role models for residents. It certainly seems plausible that the stress felt by program directors contributes to the development of resident stress.

The Pediatric Special Requirements of the Accreditation Council on Graduate Medical Education[8] state that the program director "must be capable of administering the program in an effective manner and be competent in the care of pediatric patients. He/she should have demonstrated ability as a teacher and be knowledgeable in the related basic sciences and in research methodology. The director should be certified by the American Board of Pediatrics or should possess suitable equivalent qualifications."

Our results document the perceived needs of program directors for organized training in specific content areas, such as curriculum design, budgetary processes, and Residency Review Committee requirements, as well as in such areas as motivational techniques, skills of conflict management, and evaluating residents and giving them feedback. Such courses exist for other physician managers and it seems both feasible and reasonable that they be developed for residency program directors. Continuity is an important factor in the leadership of residency training, according to the Accreditation Council on Graduate Medical Education.[8] A program director management training program might lessen the rate of turnover of program directors and promote growth of continuity and expertise in this role, with attendant improvement in the quality of residency training.

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8. Special requirements for programs in pediatrics. In: *1989-90 Directory of Graduate Medical Education Programs.* Chicago, Ill: American Medical Association; 1989:87.

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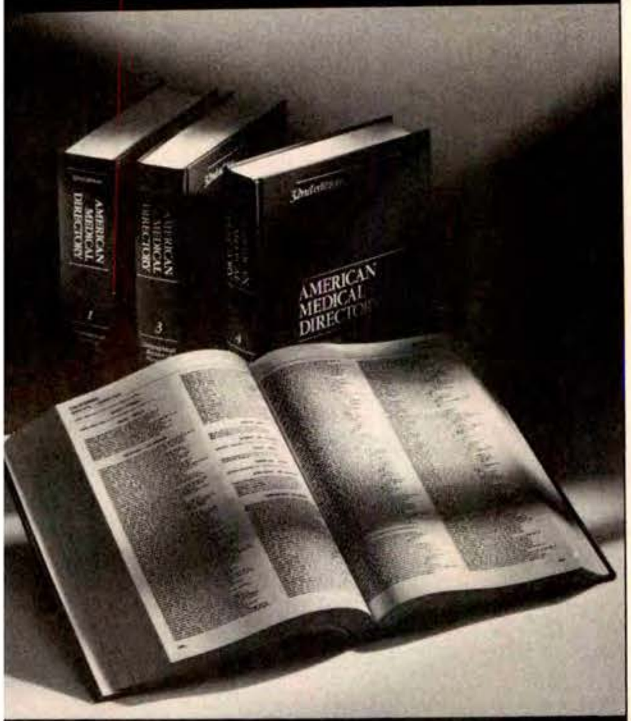

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BRIEF SUMMARY OF PRESCRIBING INFORMATION

INDICATIONS: CHILDREN'S ADVIL® SUSPENSION is indicated for the reduction of fever in patients aged 12 months and older, and for the relief of mild-to-moderate pain in patients aged 12 years and older.

CHILDREN'S ADVIL® SUSPENSION is also indicated for relief of the signs and symptoms of juvenile arthritis, rheumatoid arthritis, and osteoarthritis.

CHILDREN'S ADVIL® SUSPENSION is indicated for the relief of primary dysmenorrhea.

CONTRAINDICATIONS: Patients hypersensitive to ibuprofen or patients with all or part of the syndrome of nasal polyps, angioedema, and bronchospastic reactivity to aspirin or other nonsteroidal anti-inflammatory agents. Anaphylactoid reactions to ibuprofen have occurred in such patients.

WARNINGS: Risk of GI Ulcerations, Bleeding, and Perforation with NSAID Therapy: Physicians should remain alert for ulceration and bleeding in patients treated chronically with NSAIDS even in the absence of previous GI tract symptoms. In patients observed in clinical trials of several months' to two years' duration, symptomatic upper GI ulcers, gross bleeding or perforation appear to occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for one year.

Except for a prior history of serious GI events and other risk factors known to be associated with peptic ulcer disease, no risk factors have been associated with increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less well than other individuals and most spontaneous reports of fatal GI events are in this population.

PRECAUTIONS: General: Because serious GI tract ulceration and bleeding can occur without warning symptoms, physicians should follow chronically treated patients for the signs and symptoms of ulceration and bleeding.

Blurred and/or diminished vision, scotomata, and/or changes in color vision have been reported. If a patient develops such complaints the drug should be discontinued and the patient should have an ophthalmologic examination.

Fluid retention and edema have been reported with ibuprofen; therefore, the drug should be used with caution in patients with a history of cardiac decompensation or hypertension.

Ibuprofen can inhibit platelet aggregation and prolong bleeding time. CHILDREN'S ADVIL® SUSPENSION should be used with caution in persons with intrinsic coagulation defects and those on anticoagulant therapy.

The antipyretic and anti-inflammatory activity of ibuprofen may reduce fever and inflammation, thus diminishing their utility as diagnostic signs in detecting complications of presumed noninfectious, noninflammatory painful conditions.

Small decreases (usually not exceeding one gram) in hemoglobin and hematocrit with an apparent dose response relationship have been observed following chronic administration. If there are no signs of bleeding, it is probably not clinically important.

To avoid exacerbation of disease or adrenal insufficiency, patients on prolonged corticosteroid therapy should have their therapy tapered slowly when CHILDREN'S ADVIL® SUSPENSION is added to the treatment program.

Aseptic meningitis: Aseptic meningitis with fever and coma has been observed on rare occasions in adult patients on ibuprofen therapy. Although it is more likely to occur in patients with systemic lupus erythematosus and related connective tissue diseases, it has been reported in adult patients who do not have underlying chronic disease. If signs or symptoms of meningitis develop in a patient on CHILDREN'S ADVIL® SUSPENSION, the possibility of its being related to ibuprofen should be considered.

Renal Effects: As with other nonsteroidal anti-inflammatory drugs, long-term administration of ibuprofen to animals has resulted in renal papillary necrosis and other abnormal renal pathology. In humans, there have been reports of acute interstitial nephritis with hematuria, proteinuria, and occasionally nephrotic syndrome.

A second form of renal toxicity has been seen in patients with prerenal conditions leading to reduction in renal blood flow or blood volume. In these patients, administration of a nonsteroidal anti-inflammatory drug may cause a dose dependent reduction in prostaglandin formation and precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, and those taking diuretics and the elderly. Those patients at high risk who chronically take CHILDREN'S ADVIL® SUSPENSION should have renal function monitored if they have signs or symptoms of azotemia. Discontinuation of nonsteroidal anti-inflammatory drug therapy is typically followed by recovery to the pretreatment state.

Since ibuprofen is eliminated primarily by the kidneys, patients with significantly impaired renal function should be closely monitored and a reduction in dosage should be anticipated to avoid drug accumulation.

Information for Patients: Physicians may wish to discuss with their patients the potential risks and likely benefits of treatment with CHILDREN'S ADVIL® SUSPENSION.

Laboratory Tests: Meaningful (3 times the upper limit of normal) elevations of SGPT or SGOT (AST) occurred in controlled clinical trials in less than 1% of patients. A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of more severe hepatic reactions while on therapy with ibuprofen. If abnormal liver tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur, CHILDREN'S ADVIL® SUSPENSION should be discontinued.

Diabetes: Each 5 mL of CHILDREN'S ADVIL® SUSPENSION contains 2.5 g of sucrose which should be taken into consideration when treating patients with impaired glucose tolerance. It also contains 350 mg of sorbitol per 5 mL. Although in clinical trials CHILDREN'S ADVIL® SUSPENSION was not associated with more diarrhea than control treatments, should a patient develop diarrhea, the physician may wish to review the patient's dietary intake of sorbitol from other sources.

Drug Interactions: *Coumarin-type Anticoagulants:* Bleeding has been reported when ibuprofen and other nonsteroidal anti-inflammatory agents have been administered to patients on coumarin-type anticoagulants; the physician should be cautious when administering CHILDREN'S ADVIL® SUSPENSION to patients on anticoagulants.

Aspirin: Concurrent use of aspirin is not recommended.

Methotrexate: In vitro studies indicate that ibuprofen could enhance the toxicity of methotrexate. Caution should be used if CHILDREN'S ADVIL® SUSPENSION is administered concomitantly with methotrexate.

H_2 Antagonists: In studies with human volunteers, coadministration of cimetidine or ranitidine with ibuprofen had no substantive effect on ibuprofen serum concentrations.

Furosemide: Ibuprofen can reduce the natriuretic effect of furosemide and thiazides in some patients. During concomitant therapy with CHILDREN'S ADVIL® SUSPENSION, the patient should be observed closely for signs of renal failure as well as to assure diuretic efficacy.

Lithium: Ibuprofen produced an elevation of plasma lithium levels (15%) and a reduction in renal lithium clearance (19%) in a study of 11 normal volunteers during the period of concomitant drug administration. Patients should be observed carefully for signs of lithium toxicity. Read package insert for lithium before its use.

Pregnancy: Administration of ibuprofen is not recommended during pregnancy or for use by nursing mothers.

Infants: Safety and efficacy of CHILDREN'S ADVIL® SUSPENSION in children below the age of 12 months have not been established.

ADVERSE REACTIONS: The most frequent type of adverse reaction occurring with CHILDREN'S ADVIL® SUSPENSION is gastrointestinal. In clinical trials among adults involving chronic administration of ibuprofen, the percentage of patients reporting one or more gastrointestinal complaints ranged from 4% to 16%.

Incidence Greater Than 1% (but less than 3%), Probable Causal Relationship (see PRECAUTIONS): Abdominal cramps or pain, abdominal distress, constipation, diarrhea, epigastric pain,* fullness of the GI tract (bloating and flatulence), heartburn,* indigestion, nausea,* nausea and vomiting; dizziness,* headache, nervousness; pruritus, rash* (including maculopapular type); tinnitus; decreased appetite; edema, fluid retention (generally responds promptly to drug discontinuation).

Precise Incidence Unknown (but less than 1%), Probable Causal Relationship (see PRECAUTIONS): Abnormal liver function tests, gastric or duodenal ulcer with bleeding and/or perforation, gastritis, gastrointestinal hemorrhage, hepatitis, jaundice, melena, pancreatitis; alopecia, erythema multiforme, Stevens-Johnson syndrome, urticaria, vesiculobullous eruptions; aseptic meningitis with fever and coma, confusion, depression, emotional lability, insomnia, somnolence; amblyopia (blurred and/or diminished vision, scotomata and/or changes in color vision), hearing loss; agranulocytosis, aplastic anemia, decreases in hemoglobin and hematocrit, eosinophilia, hemolytic anemia (sometimes Coombs' positive), neutropenia, thrombocytopenia with or without purpura; congestive heart failure in patients with marginal cardiac function, elevated blood pressure, palpitations; anaphylaxis, bronchospasm (see CONTRAINDICATIONS), syndrome of abdominal pain, fever, chills, nausea and vomiting; acute renal failure in patients with pre-existing significantly impaired renal function, azotemia, cystitis, decreased creatinine clearance, hematuria, polyuria; dry eyes and mouth, gingival ulcers, rhinitis.

Precise Incidence Unknown (but less than 1%), Causal Relationship Unknown: Dream abnormalities, hallucinations, paresthesias, pseudotumor cerebri, photoallergic skin reactions, toxic epidermal necrolysis; cataracts, conjunctivitis, diplopia, optic neuritis; bleeding episodes (e.g., epistaxis, menorrhagia); acidosis, gynecomastia, hypoglycemic reactions; arrhythmias (sinus tachycardia, sinus bradycardia); angioedema, Henoch-Schönlein vasculitis, lupus erythematosus syndrome, serum sickness; renal papillary necrosis.

*Reactions occurring in 3% to 9% of adult patients treated with ibuprofen.

OVERDOSAGE: Patients with a history of ingestion of greater than 100 mg/kg should have induced emesis or gastric lavage. Multiple dose oral administration of activated charcoal may be useful. Supportive therapy may include oxygen, respiratory support, and parenteral fluids. Because the drug is acidic and excreted in the urine, administration of sodium bicarbonate and induction of diuresis may be beneficial.

DOSAGE AND ADMINISTRATION: Fever: 5 mg/kg if baseline temperature is 102.5°F or below or 10 mg/kg if baseline temperature is greater than 102.5°F, every 6-8 hours (children); 400 mg every 4-6 hours (adults).

Mild to moderate pain in adults: 400 mg every 4 to 6 hours.
Juvenile Arthritis: 30-40 mg/kg day in 3 or 4 divided doses.
RA and OA: 1200-3200 mg per day in 3 or 4 divided doses.
Dysmenorrhea: 400 mg every 4 hours.

HOW SUPPLIED: 4 and 16 oz. bottles

Caution: Federal law prohibits dispensing without prescription.

References:

1. Walson PD, Galletta G, Braden NJ, Alexander L. Ibuprofen, acetaminophen, and placebo treatment of febrile children. *Clin Pharmacol Ther.* 1989;46:9-17.
2. Independent Clinical Study: Reduction of Fever in Children, Multiple Dose. Data on file, Medical Department, Whitehall Laboratories.
3. Independent Clinical Study: Reduction of Fever in Children, Single Dose. Data on file, Medical Department, Whitehall Laboratories.

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For duration of fever relief, ibuprofen 10 mg/kg was proven more effective than acetaminophen 10 mg/kg —relief lasted up to 8 hours.[1,2]

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Please see brief summary of Prescribing Information on the next page.

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1. Walson PD et al. Ibuprofen, acetaminophen, and placebo treatment of febrile children. *Clin Pharmacol Ther.* 1989;46:9-17. 2. Data on file, McNeil Consumer Products Company.

Superior reduction for fevers over 102.5°F

PediaProfen™

Ibuprofen Suspension 100 mg/5 ml

The following is a brief summary only. Before prescribing, see complete prescribing information in **PediaProfen** labeling.

INDICATIONS AND USAGE: PediaProfen is indicated for the reduction of fever in patients aged 6 months and older, and for the relief of mild-to-moderate pain in patients aged 12 years and older.

CLINICAL PHARMACOLOGY: Controlled clinical trials comparing doses of 5 and 10 mg/kg ibuprofen and 10-15 mg/kg of acetaminophen have been conducted in children 6 months to 12 years of age with fever primarily due to viral illnesses. In these studies there were no differences between treatments in fever reduction for the first hour and maximum fever reduction occurred between 2 and 4 hours. Response after 1 hour was dependent on both the level of temperature elevation as well as the treatment. In children with baseline temperatures at or below 102.5°F, both ibuprofen doses and acetaminophen were equally effective in their maximum effect. In those children with temperatures above 102.5°F, the ibuprofen 10 mg/kg dose was more effective. By 6 hours children treated with ibuprofen 5 mg/kg tended to have recurrence of fever, whereas children treated with ibuprofen 10 mg/kg still had significant fever reduction at 8 hours. In control groups treated with 10 mg/kg acetaminophen, fever reduction resembled that seen in children treated with 5 mg/kg of ibuprofen, with the exception that temperature elevation tended to return 1-2 hours earlier.

CONTRAINDICATIONS: PediaProfen should not be used in patients who have previously exhibited hypersensitivity to ibuprofen, or in individuals with all or part of the syndrome of nasal polyps, angioedema and bronchospastic reactivity to aspirin or other nonsteroidal anti-inflammatory agents. Anaphylactoid reactions have occurred in such patients.

WARNINGS: Risk of GI Ulceration, Bleeding and Perforation with NSAID Therapy. Serious gastrointestinal toxicity such as bleeding, ulceration, and perforation, can occur at any time, with or without warning symptoms, in patients treated chronically with NSAID therapy. Although minor upper gastrointestinal problems, such as dyspepsia, are common, usually developing early in therapy, physicians should remain alert for ulceration and bleeding in patients treated chronically with NSAIDs even in the absence of previous GI tract symptoms. In patients observed in clinical trials of several months to two years duration, symptomatic upper GI ulcers, gross bleeding or perforation appear to occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for one year. Physicians should inform patients about the signs and/or symptoms of serious GI toxicity and what steps to take if they occur.

Studies to date have not identified any subset of patients not at risk of developing peptic ulceration and bleeding. Except for a prior history of serious GI events and other risk factors known to be associated with peptic ulcer disease, such as alcoholism, smoking, etc., no risk factors (e.g., age, sex) have been associated with increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less well than other individuals and most spontaneous reports of fatal GI events are in this population. Studies to date are inconclusive concerning the relative risk of various NSAIDs in causing such reactions. High doses of any NSAID probably carry a greater risk of these reactions, although controlled clinical trials showing this do not exist in most cases. In considering the use of relatively large doses (within the recommended dosage range), sufficient benefit should be anticipated to offset the potential increased risk of GI toxicity.

PRECAUTIONS: General: Blurred and/or diminished vision, scotomata, and/or changes in color vision have been reported. If a patient develops such complaints while receiving **PediaProfen**, the drug should be discontinued and the patient should have an ophthalmologic examination which includes central visual fields and color vision testing.

Fluid retention and edema have been reported in association with ibuprofen; therefore, the drug should be used with caution in patients with a history of cardiac decompensation or hypertension.

PediaProfen, like other nonsteroidal anti-inflammatory agents, can inhibit platelet aggregation, but the effect is quantitatively less and of shorter duration than that seen with aspirin. Ibuprofen has been shown to prolong bleeding time (but within the normal range) in normal subjects. Because this prolonged bleeding effect may be exaggerated in patients with underlying hemostatic defects, **PediaProfen** should be used with caution in persons with intrinsic coagulation defects and those on anticoagulant therapy.

Patients on **PediaProfen** should report to their physicians signs or symptoms of gastrointestinal ulceration or bleeding, blurred vision or other eye symptoms, skin rash, weight gain, or edema.

In order to avoid exacerbation of disease of adrenal insufficiency, patients who have been on prolonged corticosteroid therapy should have their therapy tapered slowly rather than discontinued abruptly when ibuprofen is added to the treatment program.

The antipyretic and anti-inflammatory activity of **PediaProfen** may reduce fever and inflammation, thus diminishing their utility as diagnostic signs in detecting complications of presumed noninfectious, noninflammatory painful conditions.

Since ibuprofen is eliminated primarily by the kidney, patients with significantly impaired renal function should be closely monitored and a reduction in dosage should be anticipated to avoid drug accumulation. Prospective studies on the safety of ibuprofen in patients with chronic renal failure have not been conducted.

Safety and efficacy of **PediaProfen** in children below the age of 6 months has not been established.

Pregnancy: Reproductive studies conducted in rats and rabbits at doses somewhat less than the maximal clinical dose did not demonstrate evidence of developmental abnormalities. However, animal reproduction studies are not always predictive of human response. As there are no adequate and well-controlled studies in pregnant women, this drug should be used during pregnancy only if clearly needed. Because of the known effects of nonsteroidal anti-inflammatory drugs on the fetal cardiovascular system (closure of ductus arteriosus), use during late pregnancy should be avoided. As with other drugs known to inhibit prostaglandin synthesis, an increased incidence of dystocia and delayed parturition occurred in rats. Administration of **PediaProfen** is not recommended during pregnancy.

ADVERSE REACTIONS: The most frequent type of adverse reaction occurring with ibuprofen is gastrointestinal. In controlled clinical trials, the percentage of adult patients reporting one or more gastrointestinal complaints ranged from 4% to 16%.

Adverse reactions occurring in 3% to 9% of patients treated with ibuprofen: nausea, epigastric pain, heartburn, dizziness, rash. *Adverse reactions occurring in 1% to 3% of patients:* diarrhea, abdominal distress, nausea and vomiting, indigestion, constipation, abdominal cramps or pain, fullness of GI tract, headache, nervousness, pruritus, tinnitus, decreased appetite, edema, fluid retention (generally responds promptly to drug discontinuation). Still other reactions (less than 1 in 100) have been reported, and are detailed in the full summary of prescribing information.

DOSAGE AND ADMINISTRATION: Shake well prior to administration.

Fever Reduction in Children 6 months to 12 years of age: Dosage should be adjusted on the basis of the initial temperature level (See CLINICAL PHARMACOLOGY for a description of the controlled clinical trial results). The recommended dose is 5 mg/kg if the baseline temperature is less than 102.5 °F or 10 mg/kg if the baseline temperature is greater than 102.5°F. The duration of fever reduction is generally 6-8 hours and is longer with the higher dose. The recommended maximum daily dose is 40 mg/kg.

Mild to moderate pain: 400 mg every 4 to 6 hours as necessary for the relief of pain in adults.

In controlled analgesic clinical trials, doses of ibuprofen greater than 400 mg were no more effective than 400 mg dose.

HOW SUPPLIED: PediaProfen Ibuprofen Suspension 100 mg/5 ml (teaspoon)—
orange, berry-vanilla flavored

Bottles of 4 oz (120 ml)	NDC 0045-0469-04
Bottles of 16 oz (480 ml)	NDC 0045-0469-16

SHAKE WELL BEFORE USING. Store at room temperature.

Caution: Federal law prohibits dispensing without prescription.

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Article

Mineral Metabolism and Calcitriol Therapy in Idiopathic Juvenile Osteoporosis

Giuseppe Saggese, MD; Silvano Bertelloni, MD; Giampiero I. Baroncelli, MD;
Giuseppe Perri, MD; Andrea Calderazzi, MD

• Idiopathic juvenile osteoporosis is a rare cause of osteoporosis during childhood. We examined four children (three boys and one girl, ranging in age from 2.3 to 12.6 years) with idiopathic juvenile osteoporosis. All of these patients had normal serum calcium, ionized calcium, phosphate, magnesium, 25-hydroxyvitamin D, intact parathyroid hormone, and total and extractable calcitonin levels. 1,25-Dihydroxyvitamin D values were low in three patients and slightly decreased in one. Three children were treated with calcitriol (1,25 - dihydroxycholecalciferol) (0.50 μg/d in two and 0.25 μg/d in the other). The fourth patient was not treated because of parental refusal. Therapy reduced the fracture rate. Follow-up at 6 and 12 months showed a significant increase in bone mineralization, which reached normal values in two children after 12 months of treatment. No side effects of calcitriol therapy were observed. The untreated patient did not show an improvement of bone mineralization in the same time.

(*AJDC.* 1991;145:457-462)

Idiopathic juvenile osteoporosis (IJO) is a rare form of bone demineralization during childhood.[1] The diagnosis is difficult since symptoms are not specific; it is based on the exclusion of known causes of osteoporosis in childhood, mainly the mild forms of osteogenesis imperfecta.[1] Typical features are fractures of the long bones and of the vertebrae, bone pain, difficulty in walking, and variable time to spontaneous recovery of bone mineralization, generally within 3 to 4 years.[2-4] In most patients, the onset of disease is just before puberty.[3,4] Kooh et al[5] and Exner et al[6] described some cases in which symptoms became evident before the age of 5 years. These periods of life, ie, the early years and peripuberty, are characterized by a high height velocity,[7] and it is likely that IJO requires rapid growth to be manifest clinically.

The pathogenesis of IJO is unknown.[2] A negative calcium balance, detected in some[3,8,9] but not in all patients,[10] is the main metabolic abnormality observed. Marder and coworkers[11] found low 1,25-dihydroxyvitamin D [$1,25(\text{OH})_2\text{D}$] levels in one patient, while Leroy et al[12] found high $1,25(\text{OH})_2\text{D}$ concentrations associated with low levels of 25-hydroxyvitamin D (25-OH-D) and 24,25-dihydroxyvitamin D in the girl they observed. Recently, Jackson et al[13] suggested a possible calcitonin deficiency in some cases.

Therapeutic trials with vitamin D, calcium supplements, calcitonin, and anabolic steroids failed to modify the natural course of IJO.[3,13] Marder et al[11] found that calcitriol (1,25-dihydroxycholecalciferol) was effective, even if the same group did not confirm this finding in another patient.[13]

Since the pathogenesis of IJO has been related to an impaired secretion of $1,25(\text{OH})_2\text{D}$[11] or calcitonin,[13] we studied serum basal and stimulated levels of $1,25(\text{OH})_2\text{D}$ and calcitonin to clarify the relationships between these hormones and IJO. In this study, we evaluated both total plasma calcitonin (tCT) and extractable calcitonin (exCT) levels, since it has been demonstrated that the exCT measurement reflects more accurately the biologically relevant plasma monomeric calcitonin level than the tCT assay does.[14] Moreover, we report bone mineralization, assessed by single photon absorptiometry (SPA), at diagnosis and during 3 years of follow-up. In the first year of follow-up, three patients received calcitriol therapy; the fourth was not treated because of parental refusal.

SUBJECTS AND METHODS

Patients

We examined three boys and one girl with IJO (Table 1). Symptoms were bone pain, recurrent fractures at the methaphyses of long bones in all but one (patient 2), and difficulty in walking. In none of the patients was there any history of nausea, vomiting, recurrent diarrhea, steatorrhea, immobilization, bleeding tendency, familial osteogenesis imperfecta, or other metabolic bone disease. A detailed evaluation of diet showed an adequate intake of energy, protein, calcium, and phosphate. Roentgenographic films showed diffuse osteoporosis in the three boys only. No signs of rickets, ossa suturarum, or abnormalities of the lamina dura were present. More clinical details of these patients at diagnosis were reported elsewhere.[15]

Study Protocol

All subjects were studied in the supine position after an overnight fast; blood samples were taken from an antecubital vein through an indwelling catheter between 8 and 9 AM for the determination of calcium, phosphate, magnesium, alkaline phosphatase, osteocalcin (the major noncollagenous bone protein secreted by osteoblasts),[16] intact parathyroid hormone (PTH), tCT, exCT, 25-OH-D, and $1,25(\text{OH})_2\text{D}$ levels in basal condition. After

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From the Vitamin D Laboratory and Calcium Research Center, Endocrine Unit, Department of Pediatrics (Drs Saggese, Bertelloni, and Baroncelli), and Institute of Radiology (Drs Perri and Calderazzi), University of Pisa, Italy.

Reprint requests to Vitamin D Laboratory and Calcium Research Center, Endocrine Unit, Department of Pediatrics, University of Pisa, Via Roma, 35, 56100 Pisa, Italy (Dr Saggese).

Table 1.—Clinical and Radiological Findings

	Patient No.			
	1	2	3	4
Age, y/sex	12.1/M	2.0/M	12.6/F	9.0/M
Symptom onset, age, y	9.5	1.3	10.5	2.1
Height, cm	148	91	148	126
Height percentile*	50	75	10-25	10-25
Weight, kg	44	14	40	25
Weight percentile*	75-90	50	25	25
Pubertal stage*	G1Ph1	G1Ph1	B2Ph1	G1Ph1
Bone age, y†	12.0	1.7	10.0	9.0
Family history	No	No	No	No
Bone pain	Diffuse	Knee, foot	Diffuse	Legs, spine
Walking difficulty	Yes	No	Yes	No
Loss of height	No	No	Yes	Yes
Backache	No	Yes	No	Yes
Pigeon chest	No	Yes	No	No
Fractures	Legs, arms	No	Hands, knees, long bones	Vertebrae, long bones
Fracture rate, No./y	6	. . .	8	9
Osteoporosis (roentgenography)	Skull, sella, long bones	Widespread	No	Vertebrae, carpal and long bones

*Tanner and Whitehouse standards.[7] G, Ph, and B (pubertal stage) indicate genitalia, pubic hair, and breast.

†Gruelich and Pyle[35] method.

clotting, the serum was separated by centrifugation and the samples were aliquoted and stored in the dark at −20°C until assayed. Measurement of ionized calcium was performed on blood samples collected in anaerobic tubes that had been completely filled; after centrifugation, the serum was analyzed within 1 hour. The calcitonin levels were also measured after calcium infusion; 50 mL of isotonic saline containing calcium gluconate (2 mg of elemental calcium per kilogram of body weight) was infused intravenously during a 5-minute period.[14] Blood samples for the measurement of ionized calcium, tCT, and exCT were obtained before infusion and at 5 and 10 minutes after the beginning of the infusion. Blood for ionized calcium determination was obtained from a site distant from that of the calcium infusion. No adverse effects were observed.

A dynamic evaluation of PTH and $1,25(OH)_2D$ levels, using low-calcium diet as previously described,[17] was started 1 day later. Briefly, serum for measuring ionized calcium, intact PTH, and $1,25(OH)_2D$ was obtained; during the following 3 days, the patients assumed a low-calcium diet, providing a calcium intake of 2 mg/kg per day or less. The diet was formulated with common foods on the basis of the standard tables of foods and their mineral contents; it is effective in increasing PTH and $1,25(OH)_2D$ serum levels in normal children.[17] The diet satisfied the requirements of magnesium and phosphate; energy intakes were appropriate for age and weight. The children were studied as outpatients, and the parents were provided with quantitative daily diet instructions. The parents recorded the exact weight of eaten foods, an the daily diary diet was reviewed by one of us (S.B.). At the en of the 3-day diet, ionized calcium, intact PTH, and $1,25(OH)_2$ levels were reevaluated.

Subsequently, patients 3 and 4 were treated with 0.50 µg/d o calcitriol in two divided doses; patient 2 received 0.25 µg of cal citriol once a day. Doses were calculated on the basis of a minima daily $1,25(OH)_2D$ production rate[18] given that endogenous pro duction was present. Child 1 was not treated because the parent did not consent.

Side effects of calcitriol in the treated children were monitore measuring serum ionized calcium and urinary calcium–urinar creatinine ratio every 3 months.

Informed consent was obtained from both parents of eac child. The study was approved by the Committee for Investigations in Children of our department; one child's parents did not consent to treatment.

Methods

Serum levels of calcium (normal range, 2.1 to 2.7 mmol/L), phosphate (1.2 to 2.0 mmol/L), magnesium (0.8 to 1.3 mmol/L), alkaline phosphatase (86 to 645 U/L), glucose (4.0 to 6.4 mmol/L), creatinine (<0.88 µmol/L), alanine aminotransferase (<40 U/L), and aspartate aminotransferase (<40 U/L) were assessed by an automatic analyzer (model Chem-1 System, Technicon Instruments Co, Tarrytown, NY). The serum ionized calcium level was measured by a selective electrode (ORION SS-20, Cambridge, Mass) at 37°C and corrected for pH at 7.4 (normal level, 1.1 to 1.3 mmol/L; N = 57 healthy children). Levels of cortisol (normal value at 8 AM, 138.0 to 691.0 nmol/L; at midnight, 55 to 113 nmol/L), total thyroxine (normal level, 51.0 to 154.0 nmol/L), total triiodothyronine (normal level, 1.2 to 3.1 nmol/L), and thyrotropin (normal level, 0.6 to 6.3 mU/L) were detected by commercially available radioimmunoassays (RIAs) (Biodata, Milan, Italy).

The osteocalcin level was assayed by RIA using a commercially available kit (Osteocalcin, INCSTAR Co, Stillwater, Minn). Sensitivity was 0.2 ng/mL; interassay and intra-assay variations were 8.9% and 6.3%, respectively. Our normal values were as follows: 12.2±5.5 ng/mL for 1- to 9-year-olds; 20.8±8.5 ng/mL for 9- to 14-year-olds; and 7.3±3.4 ng/mL for 14- to 18-year-olds.[18]

Parathyroid hormone levels were measured by a two-site immunoradiometric assay for the biologically intact 1-84 amino acid chain of the hormone based on two different goat polyclonal antibodies specific for well-defined regions of the molecule (Allegro Intact PTH, Nichols Institute Diagnostics, San Juan Capistrano, Calif). Sensitivity of the method was 1 ng/L; interassay and intra-assay variations were 5.5% and 4.1%, respectively. Normal values in our laboratory were 31.2±10.8 ng/L, with no significant variations between ages.[19]

Total calcitonin levels were measured in whole serum by an RIA method based on a highly sensitive and specific antiserum capable of detecting hormone levels as low as 3 ng/L (Calcitonin, Nichols Institute Diagnostics). Sequential analysis with delayed tracer addition is employed to maximize assay sensitivity. The calcitonin standard is calibrated against the World Health Organization calcitonin preparation (code 70/234 human, synthetic), National Institute for Biological Standards and Controls, London, England. Interassay and intra-assay variations were 8.9% and 6.7%, respectively; our normal values were 25.0±15.0 ng/L.[20] Levels of exCT were evaluated by the same RIA after an extraction-concentration step performed by a slight modification of the Body and Heath[14] method. Briefly, 3 mL of serum was applied to prewashed (5 mL of distilled water minicolumns (Silica Sep-pak, Waters Associates, Milford, Mass); the cartridges were washed with acetic acid in water (4:96, vol/vol), and exCT was eluted with 3 mL of methanol in water (70:30, vol/vol). The sample was dried, redissolved in assay buffer, and measured by calcitonin RIA. An internal standard was employed to calculate the recovery of exCT after the extraction-concentration procedure. Normal values were 6.0±3.0 ng/L.[20]

Levels of 25-OH-D and $1,25(OH)_2D$ were measured by a competitive protein-binding assay after high-performance liquid chromatography purification, as previously described,[21] with minor modifications. In the $1,25(OH)_2D$ assay, we employed calf thymus receptor instead of chick intestinal receptor, because the

Table 2.—Mineralometric and Biochemical Data at Diagnosis*

	Patient No.			
	1	2	3	4
BMC, %	−23.0	−18.5	−14.0	−33.4
BMC/BW, %	−21.0	−17.6	−15.3	−40.2
Red blood cells, ×10^{12}/L	4.9	4.3	4.5	4.7
White blood cells, ×10^{9}/L	7.0	6.4	5.8	6.9
Platelets, ×10^{9}/L	210	179	156	230
Bone marrow	N	N	N	N
Glucose, mmol/L	4.5	4.3	5.0	4.0
Creatinine, μmol/L	61.7	71.0	44.2	76.9
AST, U/L	12	17	25	15
ALT, U/L	8	23	15	7
Calcium, mmol/L	2.45	2.65	2.40	2.50
Ionized calcium, mmol/L	1.17	1.16	1.13	1.22
Phosphate, mmol/L	1.22	1.42	1.25	1.69
Magnesium, mmol/L	1.22	1.06	0.91	1.06
Alkaline phosphatase, U/L	280	450	330	340
Osteocalcin, ng/mL	19.2	15.3	7.2	14.3
T_3, nmol/L	2.7	2.9	2.5	2.7
T_4, nmol/L	79.4	140.1	115.5	107.5
TSH, mU/L	2.0	3.5	2.1	2.7
Cortisol (8 AM), nmol/L	496.2	579.6	538.2	452.6
Cortisol (midnight), nmol/L	183.2	138.0	63.5	129.7
Intact PTH, ng/L	24.0	32.2	25.0	42.0
tCT, ng/L	19.5	28.0	39.0	18.6
exCT, ng/L	5.8	7.9	4.5	6.0
25-OH-D, nmol/L	102.7	88.5	76.0	85.0
1,25(OH)$_2$D, pmol/L	94.1	170.4	84.2	36.9
Karyotype	46,XY	46,XY	46,XX	46,XY

*BMC indicates bone mineral content; BW, bone width; N, normal; T, aspartate aminotransferase; ALT, alanine aminotransferase; T_3, iodothyronine; T_4, thyroxine; TSH, thyrotropin; PTH, parathyroid rmone; tCT, total plasma calcitonin; exCT, extractable calcitonin; 25-H-D, 25-hydroxyvitamin D; and 1,25(OH)$_2$D, 1,25-dihydroxyvitamin

rmer shows higher sensitivity and specificity for 1,25(OH)$_2$D.[22] e method was improved with a disequilibrium procedure us-g delayed tracer addition to test tubes to increase sensitivity. ch metabolite was measured in duplicate against a reference ndard. Interassay and intra-assay variations and sensitivity ere, respectively, 4.0%, 3.1%, and 1.3 nmol/L for 25-OH-D and 3%, 3.6%, and 5.0 pmol/L for 1,25(OH)$_2$D. Our normal values r age are as follows: for 25-OH-D, 97.0±24.2 nmol/L for ages nonth to 2.0 years; 83.0±12.0 nmol/L for ages 2.1 to 10.7 years; d 86.7±16.5 nmol/L for ages 11.0 to 17.0 years; for 1,25(OH)$_2$D, 8.0±20.0 pmol/L for ages 1 month to 2.0 years; 92.0± .5 pmol/L for ages 2.1 to 10.7 years; and 179.0±17.0 pmol/L for es 11.0 to 17.0 years.[21]

Bone mineral analysis was performed by SPA (model 2783, rland Corporation, Atkinson, Wis) at the distal third of the ndominant radius. Bone mineral content (BMC) (grams per ntimeter) and BMC/bone width (BMC/BW) (grams per square ntimeter) of each subject represented the mean of two scans. e results were calculated as percentage means of BMC and IC/BW values in respect to the values expected for sex- and e-matched normal subjects (2-year age groups).[23] The method s a coefficient of variation of 2% or lower.

Table 3.—Dynamic Evaluation of tCT, exCT, PTH, and 1,25(OH)$_2$D*

Stimulus	Levels			
	IV Calcium (2 mg/kg)			
	Patients (n=4)		Controls (n=10)	
	0 min	10 min	0 min	10 min
Ionized calcium, mmol/L	1.15±0.03	1.34±0.06†	1.17±0.05	1.39±0.09‡
tCT, ng/L	26.3±8.2	57.7±14.5§	28.4±15.5	65.7±28.9†
exCT, ng/L	6.0±1.2	24.8±5.6†	5.2±2.3	22.2±10.1‡
	Low-Calcium Diet			
	Patients (n=4)		Controls (n=13)	
	Day 1	Day 3	Day 1	Day 3
Ionized calcium, mmol/L	1.15±0.02	1.05±0.03§	1.20±0.05	1.1±0.04‡
Intact PTH, ng/L	28.4±6.0	45.1±7.5‖	32.0±11.2	52.1±15.5†
1,25(OH)$_2$D, pmol/L	90.0±32.6	103.7±25.7	110.9±9.4	168.5±13.2‡

*tCT indicates total plasma calcitonin; exCT, extractable calcitonin; PTH, parathyroid hormone; 1,25(OH)$_2$D, 1,25-dihydroxyvitamin D; and IV, intravenous. Control values for IV calcium[20] and low-calcium diet[17] were selected from previous data obtained in healthy children matched for age, sex, and vitamin D status in respect to patients.

†*P*<.01 vs 0 minutes or day 1.

‡*P*<.001 vs 0 minutes or day 1.

§*P*<.02 vs 0 minutes or day 1.

‖*P*<.05 vs day 1.

RESULTS

Mineralometric and Biochemical Data at Diagnosis

Bone mineralization and biochemical data at diagnosis are reported in Table 2. Bone mineral analysis showed a reduction of both BMC and BMC/BW in patients with IJO in respect to our age- and sex-matched normal values.

Levels of calcium, ionized calcium, phosphate, magnesium, alkaline phosphatase, glucose, creatinine, alanine aminotransferase, aspartate aminotransferase, cortisol (basal and circadian rhythm), triiodothyronine, thyroxine, and thyrotropin were in the normal range; the level of osteocalcin was low in patient 3 and normal in the others. The concentration of 1,25(OH)$_2$D was reduced in three subjects (patients 1, 3, and 4) and slightly decreased in the last one (patient 2); the other examined measures were in the normal range (Table 2).

The calcium stimulation test showed a normal secretory reserve of tCT and exCT (Table 3). While receiving a low-calcium diet, the patients' ionized calcium values fell and intact PTH levels rose, as in healthy subjects, but 1,25(OH)$_2$D concentrations did not increase (Table 3).

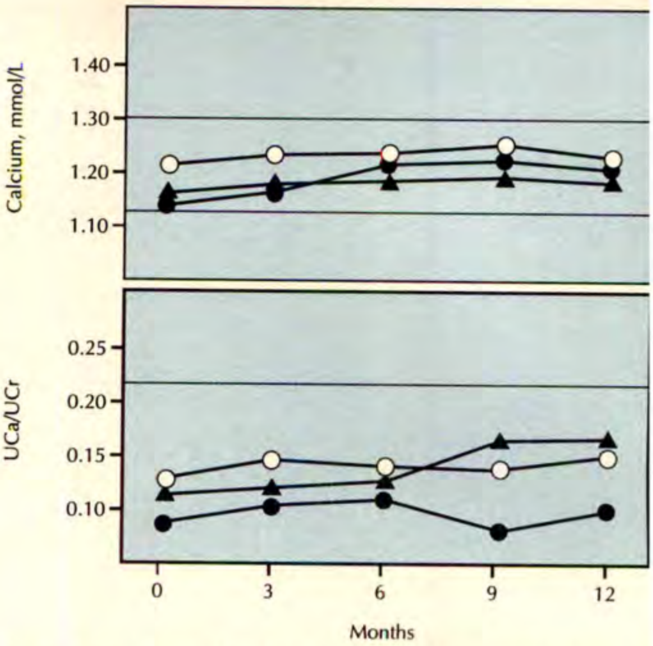
Follow-up

Calcitriol administration in the treated patients reduced the frequency of fractures and resulted in improvement of the clinical symptoms, which disappeared within 5 to 9 months. During the first month of treatment, patients remained in their homes to minimize the opportunity for trauma, and no fractures occurred. In the following 6 months, two adjunctive fractures were experienced by patient 4 (one from major trauma in a bicycle accident, the second from intensive physical activity) and one by patient

Table 4.—Bone Mineral Data During Follow-up*

Bone Loss, mo	Patient No.			
	1	2	3	4
6				
BMC	−27.0	−9.3	−5.2	−18.0
BMC/BW	−25.1	−7.4	−15.1	−24.2
12				
BMC	−22.5	−2.4	N	−7.5
BMC/BW	−18.7	N	−4.1	−10.5
18				
BMC	−23.0	+3.7	N	...
BMC/BW	−27.8	+4.0	N	...
24				
BMC	−20.2	+5.0	N	...
BMC/BW	−18.7	N	+4.5	...
30				
BMC	−13.3	−5.2	N	...
BMC/BW	−16.6	N	+6.7	...
36				
BMC	...	+5.1	N	...
BMC/BW	...	+6.2	N	...

*BMC indicates bone mineral content; BW, bone width; and N, normal. Values are percent. Patient 1 stopped follow-up after 30 months; patient 4 discontinued therapy and follow-up after 12 months.



Serum ionized calcium levels and urinary calcium excretion (urinary calcium–urinary creatinine ratio [UCa/UCr]) in the three patients with idiopathic juvenile osteoporosis during calcitriol treatment. Open circles indicate patient 2; solid circles, patient 3; and triangles, patient 4.

3 (traumatic metacarpal fracture). Additional fractures did not occur for the remaining period of observation. After 6 months of treatment, BMC and BMC/BW increased in all treated subjects (Table 4). After 1 year of therapy, bone mineralization reached normal values in patients 2 and 3; patient 4 also showed a clear improvement of BMC and BMC/BW. After this control period, patient 4 discontinued care, and no other data are available. In the other two treated children (patients 2 and 3), BMC and BMC/BW increased in the subsequent 2 years according to age-related increments (Table 4), and no other fractures were experienced by these patients.

No side effects of calcitriol therapy were observed. The serum ionized calcium level and urinary calcium–urinary creatinine ratio remained in the normal range in the three patients during treatment (Figure).

The untreated boy (patient 1) showed a slow increment of mineralization with no improvement at 1 year of follow-up and with only a slight increase of bone mineralization 30 months after the initial evaluation (Table 4). During this period, fractures occurred with the same rate as before the initial evaluation (3 to 5 fractures per year).

COMMENT

Diagnosis of IJO in our patients was made by the presence of typical skeletal involvement and by ruling out the other known causes of osteoporosis in childhood on the basis of history, physical examination, and laboratory data.[2-4] Our patients showed neither the typical features of osteogenesis imperfecta (blue sclerae, lax ligaments, dental abnormalities, family history, deafness, skull abnormalities), the main differential diagnosis,[1] nor the signs or symptoms of thyrotoxicosis, Cushing's syndrome, defects in secretory activity of parathyroid glands, diabetes, connective tissue disorders, chronic rheumatic diseases, hematological malignant neoplasm, malabsorption syndromes, or chromosomal disorders. Vitamin D deficiency was ruled out by history of sufficient solar exposure and normal serum 25-OH-D levels, the best index of individual vitamin D status.[24] Dietetic deprivation was excluded by patient history, which showed adequate calcium and phosphate intake. Moreover, skeletal fractures, occurring mainly at metaphyseal sites, are pathognomonic of IJO.[3,4,25-27]

Bone demineralization is the constant finding in all described cases of IJO.[1,2] Radiological evidence of osteoporosis was present in only three of our children; in one (patient 3), bone loss was evident only when assessed by SPA, suggesting that in cases of children with a history evoking IJO but with normal roentgenograms, a more sensitive evaluation of skeletal mineral content is required. Furthermore, SPA may allow a more accurate follow-up of bone mineralization if some kind of treatment is employed. The lack of fractures, first reported by Lapatsanis et al[9] in patients with IJO, was found by us in one boy (patient 2).

The pathogenesis of IJO is largely unknown.[2] The disease shows a fairly uniform age at presentation around the pubertal growth spurt, with spontaneous recovery after 3 to 5 years.[3,4] Moreover, some instances of childhood osteoporosis of unknown origin have been reported in the first years of life.[5,6] These patients were identical with cases of IJO in regard to symptoms, signs, radiological and biochemical findings, and course of the disease: spontaneous recovery occurred when growth velocity fell after the first 3 to 4 years of life.[5,6] Therefore, the two forms may represent an expression of the same disease,[2,5] in which rapid growth velocity acts as a trigger to make it clinically manifest.

Biochemical data in IJO are characterized by normal levels of calcium, phosphate, and alkaline phosphatase[3-5,8,10] and by a slight increase of urinary total hydroxyproline.[4] The external balance of calcium has been shown to be negative in most affected children,[3,4,8,9] zero in the mild forms, and positive in some other patients.[10] Clinical recovery from the disease is associated with the normalization of calcium balance.[4,9] Parathyroid hormone levels have been measured in the normal range,[4,10-12] as we confirmed in our patients by using an ultrasensitive assay specific for the intact PTH molecule, which allows a complete discrimination of hormone levels in patients with altered parathyroid gland secretion from levels in normal subjects.[28] Marder et al[11] underlined a severe 1,25$(OH)_2$D deficiency in the child they studied and hypothesized that the negative calcium balance could be due to reduced 1,25$(OH)_2$D levels, mostly related to a transient sex steroid deficiency before the onset of puberty. The increase of sex steroid production during puberty[29] would explain the spontaneous improvement in bone mineralization for patients with IJO, and the increase of 1,25$(OH)_2$D values in the patient of Marder et al.[11]

However, the rarity of IJO and its occurrence in some children during the first years of life point out that other factors are involved in the pathogenesis of the disease. Vitamin D deficiency, as suggested by Leroy et al,[12] is ruled out by the evidence of normal 25-OH-D values in our patients, as in others.[11,13] Also, the hypothesis of an increased 1,25$(OH)_2$D catabolism is not supported by the observation that calcitriol treatment in physiological doses is effective and that these low doses increased serum hormone concentrations into the normal range.[11] During the periods of life in which IJO mainly occurs, the 1,25$(OH)_2$D serum levels increase physiologically[30,31] to permit a greater intestinal mineral absorption needed for growth.[30] The low-calcium diet we used to test 1,25$(OH)_2$D production in IJO showed no significant hormone increase over baseline levels, while the same diet enabled determination of a significant 1,25$(OH)_2$D increase in healthy children.[17] In these patients, a partial defect of renal 1α-hydroxylase could be present that is able to maintain 1,25$(OH)_2$D levels in the normal range with usual calcium requirements but is not able to increase hormone levels when calcium needs are stressed, as in ages with higher growth velocity.[30] The relative sex steroid deficiency of prepuberty could cause enhanced bone resorption, as in postmenopausal osteoporosis, depending on bone hypersensitivity to normal PTH levels; thus, normocalcemia and normal PTH levels take place in spite of reduced 1,25$(OH)_2$D levels and negative calcium balance.[11,32]

Recently, Jackson and coworkers[13] described a girl with IJO in whom the 1,25$(OH)_2$D value was elevated and calcitonin was undetectable; the levels of these components returned to normal when the IJO resolved. The authors suggested that calcitonin deficiency may have a causative role in the pathogenesis of the disease. In our patients, both basal and calcium-stimulated tCT and exCT values, the latter being more representative of biologically active hormone,[14] were normal. These findings do not support the hypothesis of impaired calcitonin secretion in IJO, at least in our series. In this regard, it is of interest that calcitonin therapy administered to a girl described by Jackson et al[13] improved neither bone mineralization nor fracture rates. Furthermore, the possibility that a derangement of calcitonin secretion is involved in bone demineralization seems to be ruled out by the evidence that subjects with prolonged whole calcitonin deficiency did not have increased bone loss as compared with appropriate controls. Conversely, calcitonin excess did not cause increased bone mass.[33] Moreover, reduced bone mineralization did not develop in hypothyroid children with calcitonin deficiency from congenital thyroid agenesia in comparison with controls.[34]

In conclusion, our data support the evidence of decreased 1,25$(OH)_2$D serum levels in some patients with IJO. Calcitriol treatment seems to be effective in these subjects; however, since IJO is a disease that remits spontaneously, further study of treated patients will be required to draw definitive conclusions.

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BOOK REVIEW

Current Concepts in Childhood Spinal Muscular Atrophy

Edited by L. Merlini, C. Granata, and V. Dubowitz, 226 pp, $89.30, New York, NY, Springer-Verlag NY Inc, 1989.

There has been a surge of interest in neuromuscular disease in the past 2 years, sparked primarily by major genetic discoveries. While initial attention focused appropriately on Duchenne muscular dystrophy, the momentum has now swung to the spinal muscular atrophies, which, the authors note, are equally frequent and no less important in childhood because of their severe handicaps and disabilities. This book covers the clinical picture, research strategies, pathogenesis, genetics, natural history, rehabilitative care, and other clinical management problems. New avenues of therapy are discussed, including attention to nutrition, respiratory care, physical and occupational therapy, and psychological management. Gloria Eng, long a pioneer in the treatment of children with this disorder, notes that the terminal course may be particularly difficult: "Every parent reacts differently when the baby has a protracted course and begins to die. At that point everyone is worn out, including the physician." "No code" status, preference of the child dying at home, and hospice care are discussed. This book provides an important update and new optimism in our understanding of the basic neurobiologic characteristics of this previously fatal disorder, along with important new avenues of treatment and hope for the future as the basic genetic origin unravels even further.

Peggy C. Ferry, MD
Section of Child Neurology
Department of Pediatrics
University of Arizona
College of Medicine
Tucson, AZ 85724

Evaluation of Bayesian Forecasting for Individualized Gentamicin Dosage in Infants Weighing 1000 g or Less

Kei Lui, MBBS, FRACP; Scott M. Bryson, MSc Pharm; Danica B. Irwin, BSc Pharm; Simon Costello, MBBS, FRACP

• We evaluated the use of Bayesian forecasting for gentamicin therapy in outborn infants weighing 1000 g or less irrespective of postnatal age. Dosages were individualized using a computer program, guided by early serum gentamicin assays after a loading dose and a database of population kinetics. Steady-state gentamicin levels achieved were compared with those from a regimen based on guidelines. A total of 26 gentamicin courses were individualized in 19 infants of 22 to 33 weeks' gestation, weighing 500 to 1000 g at 1 to 41 days of age. All steady-state trough levels were between 1 and 2.4 mg/L; peak levels were between 4.4 and 9.3 mg/L. The 95% confidence intervals were in almost identical ranges. The prevalence of toxic and suboptimal trough levels was less when compared with that of 23 gentamicin courses based on guidelines in 17 control infants. We conclude that early individualized gentamicin dosage over a range of postnatal age is a practical alternative and serum level distributions appear superior.

(*AJDC.* 1991;145:463-467)

Gentamicin is an aminoglycoside frequently used in the management of neonatal sepsis. Appropriate dosage is desirable to provide adequate treatment and to avoid drug-related toxic reactions. Low-gestation infants have a high percentage of body water and, thus, a large volume of distribution in gentamicin disposition.[1] They may require large initial doses to achieve therapeutic serum peak concentrations.[2,3] Glomerular filtration rate is the main determinant of gentamicin plasma clearance and half-life. Although there exists a significant difference in half-life among infants of different gestations, the range is considerably wider in low-gestation infants.[1,2] This may relate to the wide differences in glomerular filtration rate in infants of similar gestation.[4,5] Furthermore, sick preterm infants often have reduced gentamicin clearance.[6] Owing to the combined effects of intrarenal drug accumulation, developmental acquisition of renal competence, and the influences of disease states, there is a need for an individualized regimen in these infants.[6,7]

In this study, we report the experience of an individualized gentamicin sulfate regimen using the Bayesian forecasting in outborn infants weighing 1000 g or less. The performance in achieving steady-state serum levels within acceptable ranges was compared with the performance from a comparable group where dosages were based on guidelines.

PATIENTS AND METHODS

During a 5-month period in our outborn neonatal intensive care unit, all infants were candidates for the study if they weighed 1000 g or less when gentamicin therapy was started. Infants who had received repeated doses from other nurseries were excluded. In each study, we individualized gentamicin therapy within 24 hours of a loading dose.

All infants who received gentamicin courses based on our unit guidelines over the immediate preceding 5 months were selected for comparison. Infants younger than 7 days receive 3.5 mg/kg every 24 hours, and infants 7 days or older may receive 2.5 mg/kg every 12 or 8 hours. There is allowance for modest alteration by the house staff when renal immaturity or impairment is suspected. The clinical profiles of the two infant groups at the start of gentamicin therapy were compared. Medications or illnesses that could alter renal clearance or volume of distribution in gentamicin kinetics were documented.

Gentamicin Loading Dose and Assays for Bayesian Forecasting

Gentamicin was given intravenously as a slow bolus over 3 to 5 minutes. Following a 3.5-mg/kg loading dose of gentamicin sulfate, two serum gentamicin concentrations 6 to 11 hours apart obtained by heel prick or arterial sampling were assayed (EMIT, Syva Diagnostics, Palo Alto, Calif). The first sample was collected between 1 and 2 hours after the loading dose. In infants who had received intravenous volume expansion, blood samples were taken at least 1 hour after infusion. Infants older than 7 days were given a second dose of gentamicin sulfate (2.5 mg/kg) 12 hours after the loading dose if results of assays were not immediately available.

Bayesian Forecasting

Forecasting was performed using a computer method established in the Department of Pharmacy. The program was adopted from an adult program,[8] and the population kinetic data used were mainly derived from the previously published Glasgow cohort of preterm and term infants (gestation, 26 to 39 weeks; age, 2 to 120 days old).[9] Pharmacokinetics were described by a simplified one-compartment open model and elimination was of first-order (exponential) kinetics.

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From the Departments of Pediatrics (Drs Lui and Costello) and Pharmacy (Mr Bryson and Ms Irwin), Hospital For Sick Children, Toronto, Ontario. Dr Lui is now with the Westmead Hospital, Westmead, New South Wales, Australia.

Reprint requests to Neonatal Intensive Care Unit, Department of Pediatrics, Westmead Hospital, Westmead, New South Wales, Australia 2145 (Dr Lui).

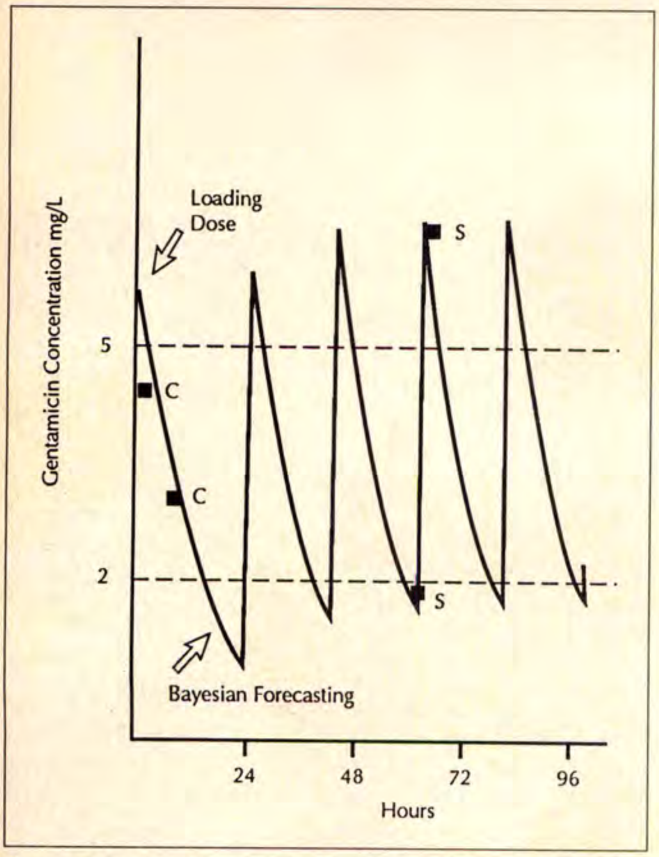

Fig 1.—*Example of Bayesian forecasting in a 27-weeks' gestation, 900-g infant who was started on gentamicin therapy on day 1. An individualized dosage of 2.6 mg (2.9 mg/kg) every 18 hours resulted in steady-state trough and peak concentrations of 1.8 mg/L and 6.7 mg/L. Computer-fitted line of gentamicin concentration is based on the Bayesian kinetic estimates in Table 1. Assayed gentamicin concentrations are also plotted for illustration. C indicates concentrations used for Bayesian forecasting; S, the measured steady-state concentrations of the implemented dosage.*

The method used population-derived kinetics as the starting point. Using three simple patient variables—gestational age, postnatal age, and current weight—the program retrieved a set of normally distributed kinetic estimates of similar clinical characteristics based on all available data from the infant population. These estimates allowed the calculation of theoretical (expected) gentamicin concentrations at any specific time (see example in Fig 1 and Table 1; this initial step is highlighted as boxed area in Table 1). Assessing the differences between the gentamicin assay results and the expected concentrations to reflect interindividual variations, the kinetic factors were adjusted by a weighting function based on the Theory of Maximum Likelihood.[10] From this most probable (Bayesian) kinetics, the steady-state levels of a given dosage were predicted. Predicted trough and peak (1 hour after dose) levels of the recommended or "optimized" dosage were targeted in the range of 1 to 2 mg/L and 5 to 7 mg/L, respectively. Dose intervals were limited to 12, 18, 24, 30, or 36 hours to make the repeated administrations practical to the nursing staff.

In infants weighing 1000 g or less at a later age when gentamicin therapy was restarted, complete forecasting procedures, including the loading doses, were carried out. With considerable changes in age and body weight, independent sets of population kinetics were retrieved for individualization.

Evaluation

To evaluate performance of the forecasting, we examined the following: (1) the 95% confidence intervals of trough and peak steady-state levels compared with the accepted ranges of gentamicin levels; (2) differences in the prevalence of "toxic" an "suboptimal" steady-state levels compared with those in the control infants; and (3) differences between predicted and measure steady-state levels, denoted as prediction bias. In both infan groups, trough and peak gentamicin levels were routinely measured around the third maintenance dose to reflect steady-stat concentrations. In our unit, trough levels between 1 and 2 mg/L and peak levels between 5 and 10 mg/L[12] are denoted as optimal We regard levels above 2.5 mg/L as toxic where dosage adjustments are mandatory consistent with the standard policy of ou unit.[13] Peak levels above 4 mg/L could be accepted as therapeutic.[11]

Table 1.—Population and Bayesian Kinetics and Steady-State Level Predictions*

Concentration Measurements			
Dose Interval	**Time From Last Dose, h**	**Measured Concentration, mg/L**	**Expected Concentration (Population)**
1	2.00	4.5	5.3
1	9.00	3.1	3.1
Parameter Estimates		**Bayesian, Mean ± SD**	**Population Mean ± SD**
Clearance		0.039 ± 0.005	0.036 ± 0.018 L/h
Volume of distribution		0.0498 ± 0.061	0.0414 ± 0.083 L
Eliminated rate constant		0.078/h	
Eliminated half-life		8.8 h	
Dose Recommendation			
Dose,		2.6 mg	
Dose interval,		18 h	
Estimated Steady-State Concentration With Recommended Dosage, mg/L			
Concentration			
Minimum,		1.7	
Maximum		6.9	
At 1 h,		6.4	
Average,		3.7	

*The population estimates (the initial step in Bayesian forecasting are highlighted as the boxed area. See text for details.

RESULTS AND ANALYSIS

Patients

A total of 30 gentamicin dosage individualizations wer performed in 23 infants weighing 1000 g or less. Four studies in four infants were excluded because gentamicin therapy was stopped or death occurred before steady state wa reached. The remaining 19 infants, 11 girls and eight boys, were of (mean±SD) 25±2 weeks' gestation (range, 22 t 33 weeks' gestation), and weighed 500 to 1000 g at birth. Among the 26 studies, 13 were entered on day 1, one wa entered on day 6, and the remaining 12 were entered between 9 and 41 days of age (including seven repeated studies at a later day).

In the preceding 5 months, 17 infants received 23 completed gentamicin courses from our routine guidelines. Their gestational age was 25±2 weeks (range, 23 to 2 weeks), and birth weight was from 630 to 1000 g. Among the 23 gentamicin courses, 12 were started on day 1, tw were started on days 5 and 6, and the remaining nine were started between days 8 and 36 (including six repeated gentamicin courses). The clinical profiles and dosages for the two groups are summarized in Table 2. Almost all infants were receiving ventilatory assistance when treatment with gentamicin was started. The indication for gentamicin, the renal function, exposure to nephrotoxic medications, and concurrent illnesses were similar.

Gentamicin Dosage

The gentamicin dose was similar between the two groups (Table 2). Dose interval of regimens guided by the

Table 2.—Summary of Clinical Profiles of Infants and Gentamicin Dosages for the Two Regimens

	Bayesian Forecasting	Standard Guideline
No. of studies	26	23
Clinical profile		
Postnatal age, d		
<7	14	14
>7	12	9
Range	1-41	1-36
Postconceptional age, wk		
Mean ± SD	26 ± 2	26 ± 1
Body weight, g		
Mean ± SD	811 ± 150	792 ± 135
Range	500-1000	630-1000
Indications		
Sepsis		
Proved	3	4
Suspected	20	17
Necrotizing enterocolitis	2	2
Need for ventilation	25	23
Nephrotoxic drugs		
Indomethacin	2	0
Vancomycin hydrochloride	3	3
Amphotericin B	0	1
Oliguria <1 mL/kg/h	1	1
Serum creatinine, μmol/L		
Mean ± SD	74 ± 32	69 ± 17
Range	42-159	44-102
Illnesses predispose to abnormal fluid accumulation		
Patent ductus arteriosus	8	5
Hydrocephalus	1	1
Gentamicin dosage		
Postnatal age <7 d		
Dose/kg, mg		
Mean ± SD	3.4 ± 0.4	3.1 ± 0.3
Range	2.7-4.2	2.5-3.5
Dose interval, h		
Mean ± SD	25 ± 7	24 ± 6
Range	12-36	12-36
Postnatal age ≥7 d		
Dose/kg, mg		
Mean ± SD	3.1 ± 0.3	2.8 ± 0.5
Range	2.9 ± 3.5	2.2-3.9
Dose interval, h		
Mean ± SD	15 ± 5	20 ± 12
Range	18-24	8-36

Bayesian forecasting ranged from 18 to 36 hours for infants younger than 7 days, and from 12 to 24 hours for postnatal age older than 7 days. In the gentamicin courses based on guidelines, dose intervals were increased by the house staff in seven instances because of clinical evidence of preexisting renal impairment or in older immature infants who had high trough levels during previous gentamicin courses. In two infants younger than 7 days who were born at 29 and 28 weeks' gestation, dose intervals were decreased to 12 and 18 hours accompanied with decreased doses per kilogram.

Steady-State Gentamicin Levels

The initial forecasting in the 19 study infants resulted in steady-state trough concentrations between 1 and 2.4 mg/L; their peak levels were between 4.7 and 9.3 mg/L. In the seven repeated studies, the trough and peak levels ranged from 1.0 to 2.3 mg/L and from 4.4 to 7.8 mg/L, respectively. The overall 95% confidence interval for trough levels was between 0.9 and 2.5 mg/L (acceptable range, 1 to 2.5 mg/L) and that of peak levels was between 4 and 9.5 mg/L (acceptable range, 4 to 10 mg/L).

In the group in which standard guidelines were used, three of 17 initial trough levels were above 2.5 mg/L (between 2.8 and 3.2 mg/L) and two were below 1 mg/L. Among the six repeated gentamicin courses, two trough levels were above 2.5 mg/L (3.4 and 3.6 mg/L) and two were less than 1 mmol/L. All 23 peak gentamicin levels, except one (3.0 mg/L), were between 5 and 9.2 mg/L. The overall 95% confidence interval for trough level was between 0.0 and 3.5 mg/L, and it was between 4 and 10 mg/L for the peak level. While the mean trough levels of the two regimens were similar, trough levels guided by Bayesian forecasting had a smaller scatter in distribution (F ratio 4.0, $P<.01$). Results are summarized in Fig 2.

Using greater than 2.5 mg/L and less than 1 mg/L as our criteria of toxic and suboptimal trough levels, prevalence of these concentrations was significantly less in regimens guided by the Bayesian forecasting (0/26 vs 5/23, $P<.01$; 0/26 vs 4/23, $P<.01$, respectively, Fisher's Exact Test). For the peak levels, we found no significant difference between the two regimens, and almost all were within acceptable range.

We found the Bayesian forecasting had a tendency to underestimate the trough and peak steady-state levels. The mean prediction bias for trough levels (predicted steady-state levels—measured levels) was −0.3 mg/L, and the mean prediction bias for peak levels was −0.4 mg/L. Results are summarized in Table 3. The prediction bias of studies entered within the first 7 days of life was considerably smaller than those studied at a later postnatal age.

COMMENT

Adequate therapy with aminoglycosides requires serum concentrations to be maintained within certain limits. Difficulties arise in patients with impaired renal function in whom serum levels decline slowly. Variable doses or variable dose frequency regimens as an adjunct to guidelines[14,15] have been suggested. However, prolonged periods of low serum levels could invite the possibility of undertreatment.[16] McCracken and Nelson[11] suggested a peak concentration of 4 to 8 mg/L and trough levels of 1 to 2 mg/L as desirable ranges for safe and effective therapy in newborn infants with impaired renal function.

In older children and adults, tables, nomograms, and computer programs based on patient variables such as weight, height, sex, and serum creatinine concentration are available to aid in aminoglycoside administration. However, assessment of renal function within the first 24 hours of life could be difficult in clinical practice. Serum creatinine concentration during this period is a reflection of the maternal renal function, while serum creatinine concentration on days 2 to 3 is a reasonable index of glomerular filtration rate in very-low-birth-weight infants.[2] Furthermore, the degree of asphyxial insult at birth is difficult to ascertain. The usefulness of Apgar scores as an indication of asphyxia in premature infants has been seriously questioned.[17]

The pharmacokinetic advantage of the Bayesian forecasting for aminoglycoside therapy has been documented

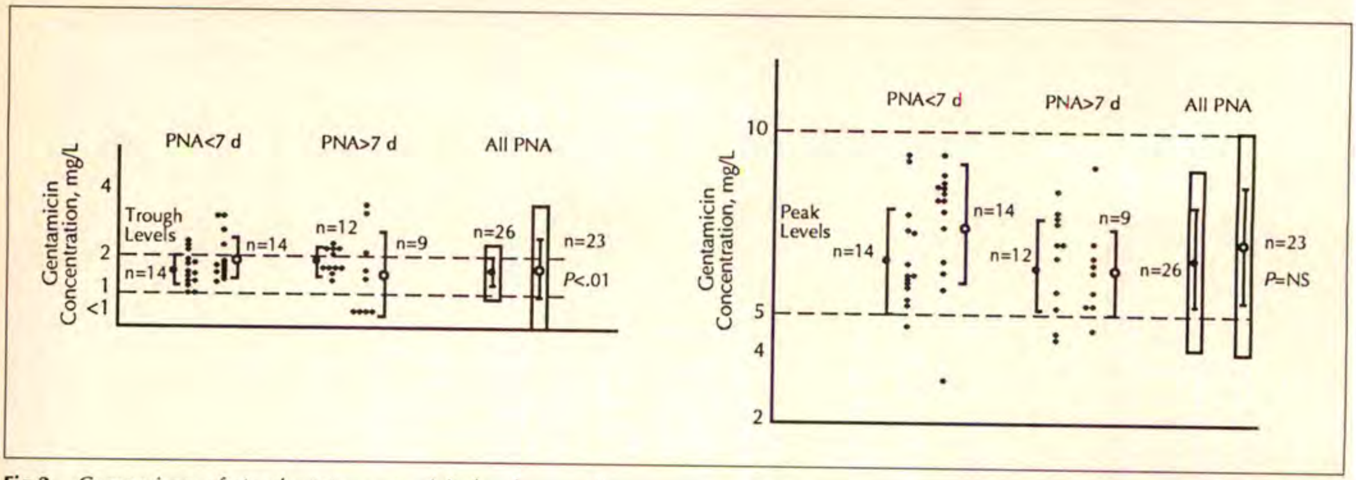

Fig 2.—*Comparison of steady-state gentamicin levels according to postnatal age (PNA) between regimens by Bayesian method and by guidelines. NS indicates not significant. Left, Trough levels. Right, Peak levels. Means and SDs are shown in closed circles for the Bayesian forecasting and in open circles for guidelines for each comparison. The 95% confidence intervals are shown in boxes.*

Table 3.—Prediction Bias of the Bayesian Forecasting Showing a Consistent Tendency of Underestimation of Steady-State Levels*

	n	Mean Predicted Gentamicin Concentration, mg/L, (Range)	Mean Prediction Bias (Predicted-Measured), mg/L, (Range)
Trough			
PNA <7 d	14	1.5 (0.8-2.1)	−0.1 (−0.9-0.5)
PNA ≥7 d	12	1.4 (0.9-1.7)	−0.5†(−1.4-0.7)
All	26	1.4 (0.8-2.1)	−0.3 (−1.4-0.7)
Peak			
PNA <7 d	14	6.1 (5.1-7.2)	−0.1 (−2.6-1.4)
PNA ≥7 d	12	5.7 (4.4-7.1)	−0.7 (−2.2-1.3)
All	26	6.1 (4.4-7.2)	−0.4 (−2.6-1.4)

*Mean and range are shown. PNA indicates postnatal age.

†Significant difference between prediction bias of trough levels at PNA <7 days and ≥7 days, Student's *t* test.

in children and adults[18-21] and in patients in the intensive care unit who exhibit considerable interindividual variations of drug disposition.[22] In reality, laboratory variations are inherent in the assay of gentamicin concentrations. This may result in errors of exponential magnitude if concentrations alone are used for kinetic extrapolations. We used three simple variables—gestation, postnatal age, and body weight—and two serum concentrations for kinetic adjustment. Bayesian theorem in this setting has the advantage that data input errors cannot easily result in misinterpretation. Therapy can be individualized from the outset and kinetics can be adjusted for the expected postnatal renal maturation. In our outborn infants weighing 1000 g or less, we achieved steady-state trough and peak levels ranging from 1 to 2.4 mg/L and from 4.4 to 9.3 mg/L, respectively. Moreover, their 95% confidence intervals were within our preset acceptable ranges.

Studies suggested the volumes of distribution were relatively consistent for infants over a small range of body weight.[2,3] When a similar total dose per body weight was used in both regimens, we were not surprised to find no significant difference in their steady-state peak levels. However, there was less variation in the trough levels from a Bayesian forecasting regimen resulting in a lower prevalence of toxic or suboptimal levels.

Seven study infants were recommenced on a regimen of gentamicin therapy at a later age. The steady-state levels appeared superior to the six repeated gentamicin courses in the control infants. Results suggest individualizing each course of gentamicin therapy to be beneficial. A guideline regimen influenced by a "previous experience" in the infant may also lead to underestimation or overestimation of the infant's renal competence.

In the first few days of life, body fluid composition and renal blood flow change considerably. Despite these, Bayesian forecasting performed well in the early postnatal ages. We suspect its performance at the older postnatal ages may improve with increased size of the population kinetic database.

Premature animals[23,24] were thought to be somewhat protected from aminoglycoside-induced nephrotoxic reactions. Recently, increasing concern has been expressed against its apparent safety.[13,25] Furthermore, optimal therapy may not only be important for infants with impaired renal function but also for infants with normal renal function. These infants may receive inadequate dosages. While the clearance of aminoglycosides is considerably decreased in this specific study population, it provides ample time for the use of Bayesian forecasting in clinical practice.

CONCLUSION

We found Bayesian forecasting for gentamicin therapy to be a practical alternative. It compared favorably with dosage based on guidelines in infants weighing 1000 g or less over a range of postnatal age, and this may potentially minimize suboptimal gentamicin treatment and dose-related toxic reactions. Serum drug level was the only factor evaluated; further studies examining clinical toxic reactions would be desirable.

Andrew W. Kelman, PhD, of Clydesoft Scientific Software provided support with the computer programming. The computer program for the Bayesian forecasting may be obtained from Mr Bryson, assistant director, Clinical Research Education Program, Department of Pharmacy, British Columbia Children's Hospital, Vancouver, or Dr A. W. Kelman, Clydesoft Scientific Software, 78 Meadows Ave, Larkmall, Lanankshire, Scotland ML9 2JG.

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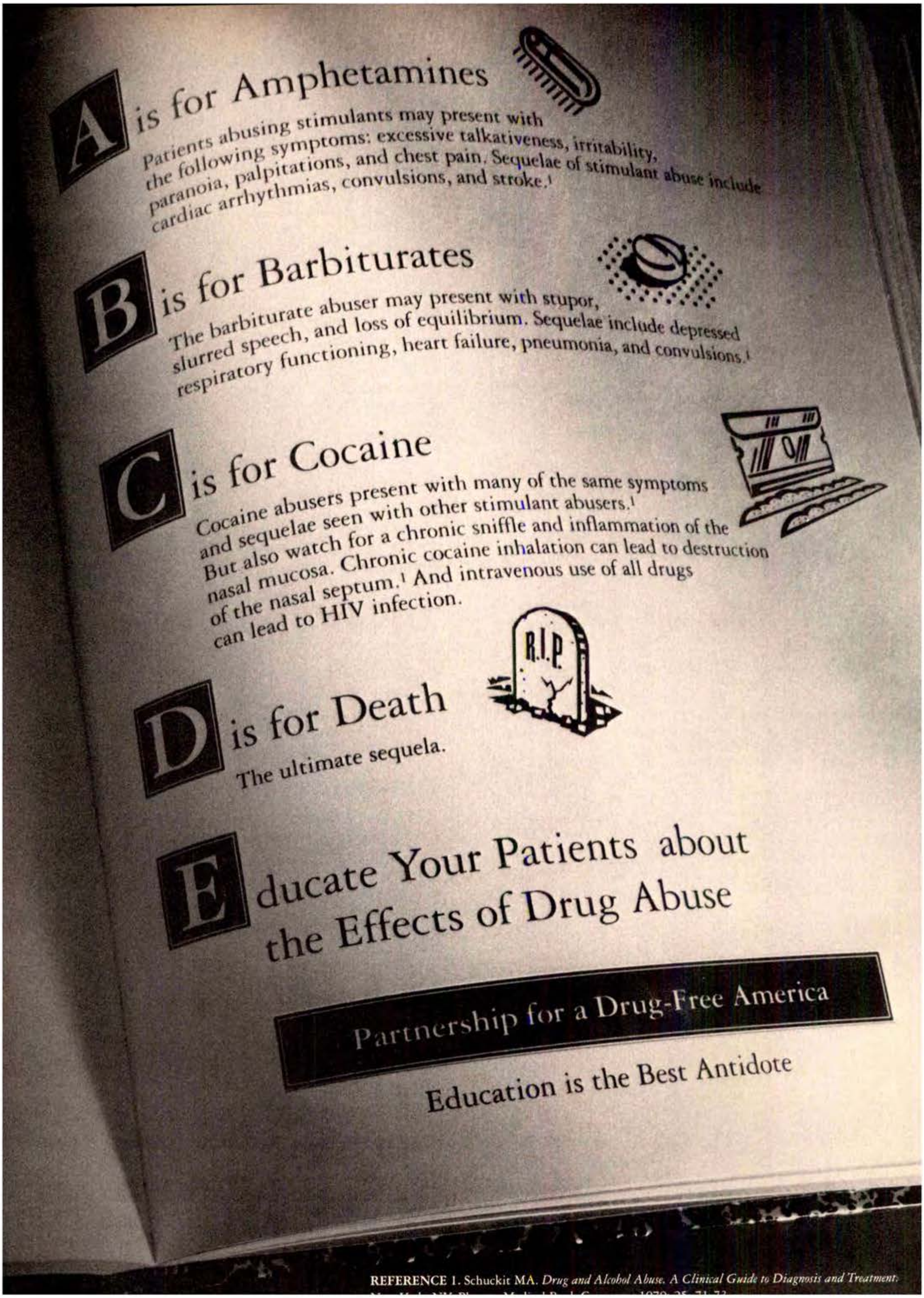

A is for Amphetamines

Patients abusing stimulants may present with the following symptoms: excessive talkativeness, irritability, paranoia, palpitations, and chest pain. Sequelae of stimulant abuse include cardiac arrhythmias, convulsions, and stroke.[1]

B is for Barbiturates

The barbiturate abuser may present with stupor, slurred speech, and loss of equilibrium. Sequelae include depressed respiratory functioning, heart failure, pneumonia, and convulsions.[1]

C is for Cocaine

Cocaine abusers present with many of the same symptoms and sequelae seen with other stimulant abusers.[1] But also watch for a chronic sniffle and inflammation of the nasal mucosa. Chronic cocaine inhalation can lead to destruction of the nasal septum.[1] And intravenous use of all drugs can lead to HIV infection.

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Warnings: Especially in infants and small children, antihistamines in overdosage may cause hallucinations, convulsions, and death.

Antihistamines may diminish mental alertness. In the young child, they may produce excitation.

Precautions: ***General:*** Because of its antihistamine component, Dimetane DX Cough Syrup should be used with caution in patients with a history of bronchial asthma, narrow angle glaucoma, gastrointestinal obstruction, or urinary bladder neck obstruction. Because of its sympathomimetic component, Dimetane DX Cough Syrup should be used with caution in patients with diabetes, hypertension, heart disease, or thyroid disease.

Information for Patients: Patients should be warned about engaging in activities requiring mental alertness, such as driving a car or operating dangerous machinery.

Drug Interactions: Antihistamines have additive effects with alcohol and other CNS depressants (hypnotics, sedatives, tranquilizers, antianxiety agents, etc.). MAO inhibitors prolong and intensify the anticholinergic (drying) effects of antihistamines. MAO inhibitors may enhance the effect of pseudoephedrine. Sympathomimetics may reduce the effects of antihypertensive drugs.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Animal studies of Dimetane DX Cough Syrup to assess the carcinogenic and mutagenic potential or the effect on fertility have not been performed.

Pregnancy

Teratogenic Effects-Pregnancy Category C

Animal reproduction studies have not been conducted with Dimetane DX Cough Syrup. It is also not known whether Dimetane DX Cough Syrup can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Dimetane DX Cough Syrup should be given to a pregnant woman only if clearly needed.

Reproduction studies of brompheniramine maleate (a component of Dimetane DX Cough Syrup) in rats and mice at doses up to 16 times the maximum human dose have revealed no evidence of impaired fertility or harm to the fetus.

Nursing Mothers: Because of the higher risk of intolerance of antihistamines in small infants generally, and in newborns and prematures in particular, Dimetane DX Cough Syrup is contraindicated in nursing mothers.

Adverse Reactions: The most frequent adverse reactions to Dimetane DX Cough Syrup are: sedation; dryness of mouth, nose and throat; thickening of bronchial secretions; dizziness. Other adverse reactions may include:

Dermatologic: Urticaria, drug rash, photosensitivity, pruritus.

Cardiovascular System: Hypotension, hypertension, cardiac arrhythmias, palpitation.

CNS: Disturbed coordination, tremor, irritability, insomnia, visual disturbances, weakness, nervousness, convulsions, headache, euphoria, and dysphoria.

G.U. System: Urinary frequency, difficult urination.

G.I. System: Epigastric discomfort, anorexia, nausea, vomiting, diarrhea, constipation.

Respiratory System: Tightness of chest and wheezing, shortness of breath.

Hematologic System: Hemolytic anemia, thrombocytopenia, agranulocytosis.

Overdosage: ***Signs and Symptoms:*** Central nervous system effects from overdosage of brompheniramine may vary from depression to stimulation, especially in children. Anticholinergic effects may be noted. Toxic doses of pseudoephedrine may result in CNS stimulation, tachycardia, hypertension, and cardiac arrhythmias; signs of CNS depression may occasionally be seen. Dextromethorphan in toxic doses will cause drowsiness, ataxia, nystagmus, opisthotonos, and convulsive seizures.

Toxic Doses: Data suggest that individuals may respond in an unexpected manner to apparently small amounts of a particular drug. A 2 1/2-year-old child survived the ingestion of 21 mg/kg of dextromethorphan exhibiting only ataxia, drowsiness, and fever, but seizures have been reported in 2 children following the ingestion of 13-17 mg/kg. Another 2 1/2-year-old child survived a dose of 300-900 mg of brompheniramine. The toxic dose of pseudoephedrine should be less than that of ephedrine, which is estimated to be 50 mg/kg.

Treatment: Induce emesis if patient is alert and is seen prior to 6 hours following ingestion. Precautions against aspiration must be taken, especially in infants and small children. Gastric lavage may be carried out, although in some instances tracheostomy may be necessary prior to lavage. Naloxone hydrochloride 0.005 mg/kg intravenously may be of value in reversing the CNS depression that may occur from an overdose of dextromethorphan. CNS stimulants may counter CNS depression. Should CNS hyperactivity or convulsive seizures occur, intravenous short-acting barbiturates may be indicated. Hypertensive responses and/or tachycardia should be treated appropriately. Oxygen, intravenous fluids, and other supportive measures should be employed as indicated.

Dosage and Administration: Adults and children 12 years of age and over: 2 teaspoonfuls every 4 hours. Children 6 to under 12 years: 1 teaspoonful every 4 hours. Children 2 to under 6 years: 1/2 teaspoonful every 4 hours. Children 6 months to under 2 years: Dosage to be established by physician.

Do not exceed 6 doses during a 24-hour period. Rev. May 1987.

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Who: Physicians and spouses who want to make a difference by being actively involved in a candidate's run for political office. *LIMIT: 32.*

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When: 8:00 am Sunday, July 14 through noon Friday, July 19,1991.

Where: Crystal City Marriott, 1999 Jefferson Davis Highway,
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How Much: *AMA Members and Federation Staff:*

AMPAC provides registration fee, course materials, daytime meals and airfare. Participants are responsible for their hotel rooms and evening meals.

Non AMA Members are responsible for their own airfare, hotel, evening meals and $1,000 registration fee.

For further information, contact Jennifer Harris, 1101 Vermont Avenue, N.W., Washington, D.C. 20005. (202) 789-7474.

SPECIAL FEATURE

Radiological Case of the Month

Janice W. Allison, MD; Carol A. Stephenson, MD; Teresita L. Angtuaco, MD;
Charles M. Glasier, MD (Contributors); *Beverly P. Wood, MD* (Section Editor)

A fetal cardiac abnormality was detected in a prenatal ultrasound examination of a 31-year-old woman. No family history of genetic syndromes or congenital heart disease was elicited, and she had two normal children. The infant, delivered by spontaneous vaginal delivery at 36 weeks' gestation, developed respiratory distress shortly after birth and was intubated.

Physical examination revealed afebrile, cyanotic female infant with tachycardia (heart rate, 116 to 152 beats per minute) and tachypnea (48 to 76 breaths per minute). Hypopigmented macules were present on her back and buttocks. The liver was palpable 3 cm below the costal margin.

An electrocardiogram revealed Wolff-Parkinson-White complex, biventricular hypertrophy, and atrial enlargement. Laboratory values were unremarkable except for hypoxia. A chest roentgenogram (Fig 1), echocardiogram, cardiac magnetic resonance imaging (MRI) (Fig 2), and cranial computed tomography (CT) (Fig 3) and MRI (Fig 4) were performed during diagnostic workup.

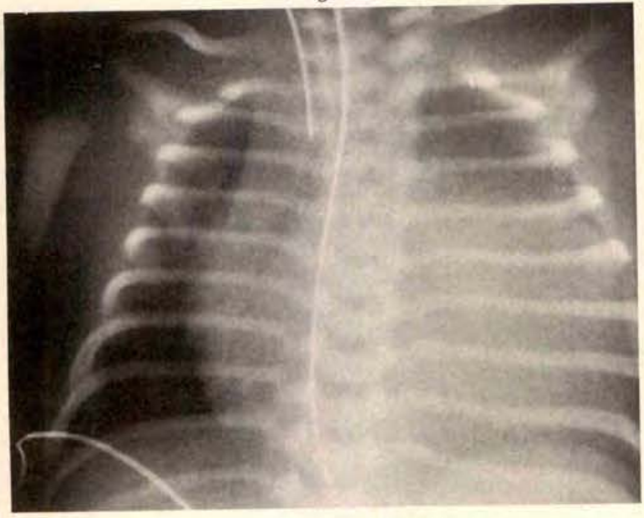
The infant's congestive heart failure was treated and she no longer required assisted ventilation by 3 days of age. On the sixth day, respiratory distress returned and the infant became cyanotic with feedings. She died of cardiac failure on the eighth day.

Accepted for publication January 23, 1991.

Contributed from the Departments of Radiology, University of Arkansas for Medical Sciences (Drs Allison and Angtuaco) and Arkansas Children's Hospital (Drs Stephenson and Glasier), Little Rock.

Reprint requests to Department of Radiology, Childrens Hospital of Los Angeles, 4650 Sunset Blvd, Los Angeles, CA 90027 (Dr Wood).

Figure 1.



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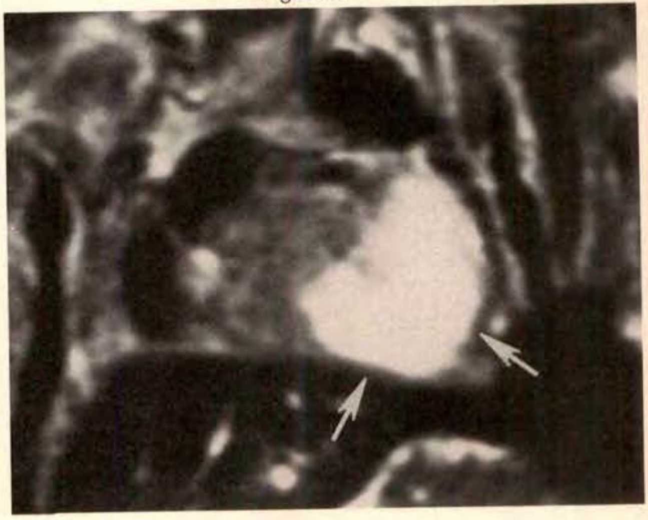

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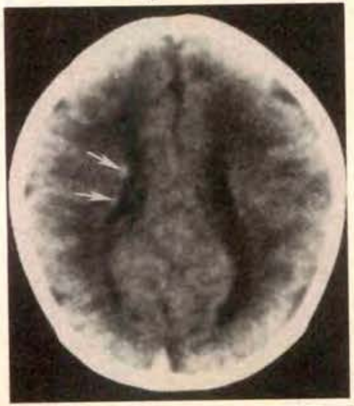

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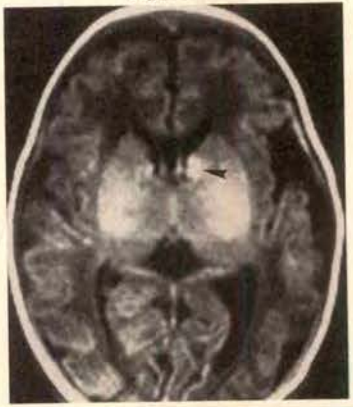

SPECIAL FEATURE

Denouement and Discussion

Tuberous Sclerosis With Myocardial and Central Nervous System Involvement at Birth

Fig 1.—*Anteroposterior chest roentgenogram reveals massive cardiomegaly.*

Fig 2.—*T1-weighted coronal magnetic resonance imaging of the chest shows a high-signal-intensity mass in the ventricular wall (arrows).*

Fig 3.—*Computed tomography of the head reveals high-density periventricular nodules (arrows).*

Fig 4.—*Axial inversion-recovery magnetic resonance imaging of the brain reveals a high-signal-intensity periventricular nodule (arrowhead). uberous sclerosis (TS) is a neurocutaneous dysplasia with clinical manifestations resulting from hamartomatous malformations of the skin, brain, heart, and kidneys. Inheritance is autosomal dominant with variable penetrance or spontaneous mutation.[1] The classic clinical triad is mental retardation, skin lesions (adenoma sebaceum or ash leaf macules), and seizures.*

This infant presented with cardiomegaly and congestive heart failure. The echocardiogram disclosed a pericardial effusion, a ventricular mass, and echogenic septal masses. Cardiac magnetic resonance imaging (MRI) and autopsy revealed multiple rhabdomyomas in the myocardium with distortion of the chambers. The largest tumor was within the septum and measured 3.2 × 3.3 cm at autopsy. Go et al[2] compared the diagnostic advantages of gated cardiac MRI with two-dimensional echocardiography in the diagnosis and characterization of intracardiac tumors in adult patients and concluded that the tumor size, shape, and surface characteristics were most specifically delineated by MRI.

In infants, 60% of primary cardiac tumors are rhabdomyomas, most commonly found in the ventricular walls, and multiple in 90% of cases. Fifty percent of infants with cardiac rhabdomyomas have TS. Seventy percent of patients with multiple rhabdomyomas die within the first year of life, and 92% die by the fifth year without surgical treatment.[3]

The most common renal abnormality associated with TS is angiomyolipoma, seen in 40% to 50% of patients. Cystic renal changes are less commonly seen in TS. Abdominal ultrasound study is indicated in all patients with TS to identify these abnormalities.

The typical cranial findings of TS include calcified periventricular subependymal nodules and low-attenuation areas (on computed tomography [CT]) in the cortex and subcortical white matter. These correspond to parenchymal hamartomas (tubers). Cortical tubers are usually found at the gray-white matter interface and may also be calcified.[4] The abnormalities noted on this infant's cranial CT were subependymal nodules (Fig 3). Sugita et al[5] described two infants with TS with intracranial calcifications detected with CT within 1 week of birth. The subependymal nodules may later transform into astrocytomas. If these occur at the foramen of Monro, they cause ventricular obstruction.[4] Astrocytomas are enhanced by intravenous contrast injection, whereas subependymal and cortical tubers are not. Therefore, routine contrast enhancement is indicated in evaluating patients with TS with CT or MRI.

The cranial MRI findings of TS include multiple cortical and subcortical regions of high signal intensity on T2-weighted images corresponding to the hypodense areas seen on CT; subependymal nodules of intermediate signal intensity on all pulse sequences; and distortion of the cortical architecture.[6] Large calcifications are seen as absent signal. Small or large calcifications are better identified with CT.[7] Subependymal nodules are demonstrated on inversion-recovery or T1-weighted images.[8] This infant's cranial MRI features were typical for TS. Subependymal nodules showed high signal intensity on inversion-recovery images and signal dropout on T2-weighted images due to calcification. Multiple areas of cortical high signal intensity were identified on the T2-weighted images.

Magnetic resonance imaging is more sensitive than CT for the detection of cerebral change in TS. Both MRI and CT are important in the early detection of TS before the clinical signs are manifested.[5] Roach et al[1] noted a correlation between the number of cortical tubers on MRI and the clinical severity of the disease as manifested by more severe developmental delay and more difficulty with seizure control. Direct correlation between the abnormalities on CT and the clinical severity of disease has not been shown.

In this infant, cranial MRI and CT were instrumental in confirming the diagnosis of TS, already suggested by the presence of multiple myocardial tumors and skin lesions. Cardiac MRI depicted extensive rhabdomyomas and ventricular distortion. These studies assisted in reaching a decision to provide palliative care because of the poor prognosis for extensive myocardial lesions. Autopsy confirmed the presence of multiple cardiac rhabdomyomas and multiple cerebral hamartomas.

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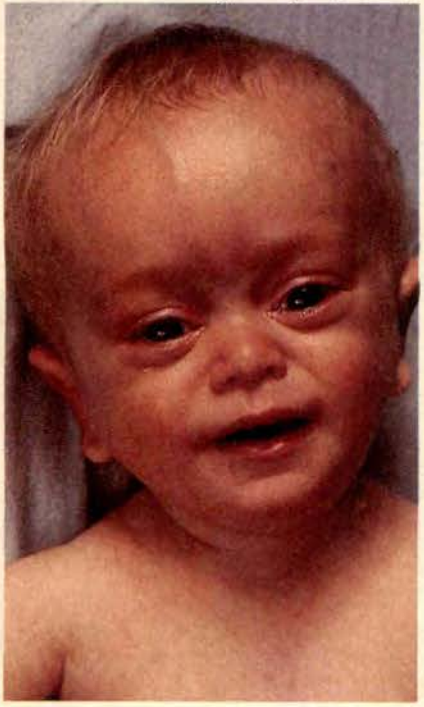
SPECIAL FEATURE

Picture of the Month

Zvi Laron, MD; Beatrice Klinger, MD; Michael Grunebaum, MD (Contributors);
Murray Feingold, MD (Editor for This Case); *Walter W. Tunnessen, MD* (Section Editor)



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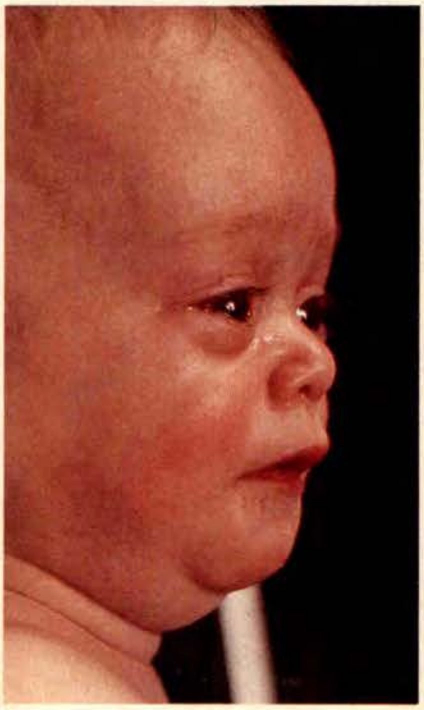

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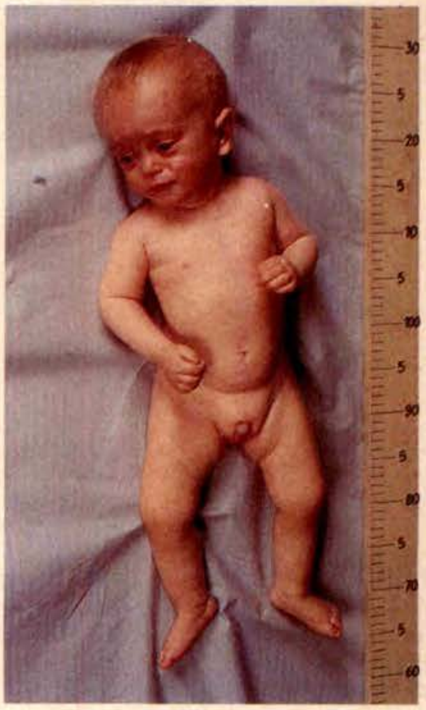

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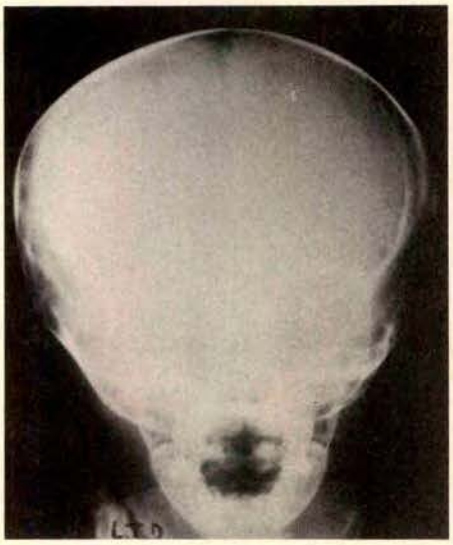

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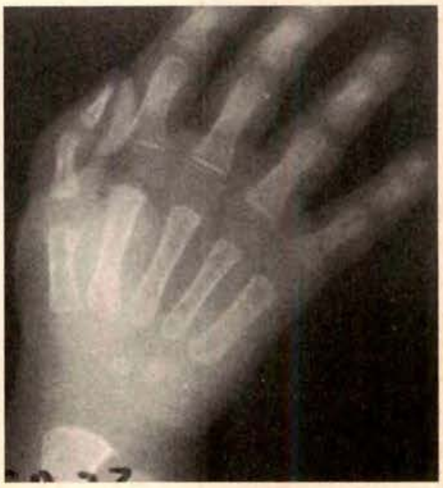

The Editors welcome contributions to Picture of the Month and Radiological Case of the Month. Those who wish to contribute should send their manuscripts to Dr Tunnessen (Picture of the Month), *The Children's Hospital of Philadelphia, 34th Street and Civic Center Blvd, Philadelphia, PA 19104, or Dr Wood* (Radiological Case of the Month), *Department of Radiology, Childrens Hospital of Los Angeles, 4650 Sunset Blvd, Los Angeles, CA 90027. Articles and photographs accepted for publication will bear the contributor's name. There is no charge for reproduction and printing of color illustrations.*

Accepted for publication December 12, 1990.

Contributed from the Institute of Pediatric and Adolescent Endocrinology (Drs Laron and Klinger) and Department of Pediatric Roentgenology (Dr Grunebaum), Beilinson Medical Center, Petah Tikva and Sackler Faculty of Medicine, Tel Aviv (Israel) University.

Reprint requests to National Birth Defects Center, Franciscan Children's Hospital, 30 Warren St, Brighton, MA 02135 (Dr Feingold).

Denouement and Discussion

Laron-Type Dwarfism

Figs 1 and 2.— *3 1/2-year-old boy with Laron-type dwarfism with sparse hair, frontal bossing, prominent veins, saddle nose, micrognathia, and small facial bones.*

Fig 3.—*Obesity and micropenis.*

Fig 4.—*Underdevelopment of facial bones and small bicondylar diameter.*

Fig 5.—*Marked retardation in skeletal maturation.*

Manifestations

Laron-type dwarfism is characterized by marked growth retardation, acromicria (small hands, feet, and chin), obesity, and micropenis. Craniofacial abnormalities include a protruding forehead, saddle nose, and an increased biparietal-bicondylar ratio, all caused by marked underdevelopment of the facial bones. Head circumference is decreased, skeletal maturation is markedly retarded, the bones are very thin, and there is an increased incidence of minor skeletal abnormalities such as slipped femoral epiphyses and Legg-Calve-Perthes disease. The obesity is generalized and there is underdevelopment of muscle mass. Genitalia and gonads are small, and puberty is delayed but ultimately attained. Final height ranges between 110 and 138 cm. Afflicted children have a typically high-pitched voice and are clinically indistinguishable from patients with growth hormone deficiency.

Biochemical abnormalities are characterized by hypoglycemia, often symptomatic at an early age, high circulating levels of growth hormone, and low serum insulinlike growth factor levels that do not rise with the administration of exogenous human growth hormone There is resistance to growth hormone due to a defect in growth hormone receptors.

Genetics

Laron-type dwarfism is a hereditary disease occurring mainly in children of Jewish, Oriental, Arab, Spanish, Portuguese, and Italian descent. However, patients have been diagnosed in white, Japanese, and Eskimo populations. Because the extracellular part of the growth hormone receptor is identical to the circulating growth hormone–binding protein, it is possible to diagnose homozygous patients and identify heterozygote carriers.

Treatment

The recent recombinant biosynthesis of insulinlike growth factor 1 has resulted in therapeutic trials aimed at replacing the hormone that the body cannot generate. Nutritional counseling is also needed to prevent hypoglycemia and progressive obesity. Continuous psychosocial counseling of the parents and patients may be indicated.

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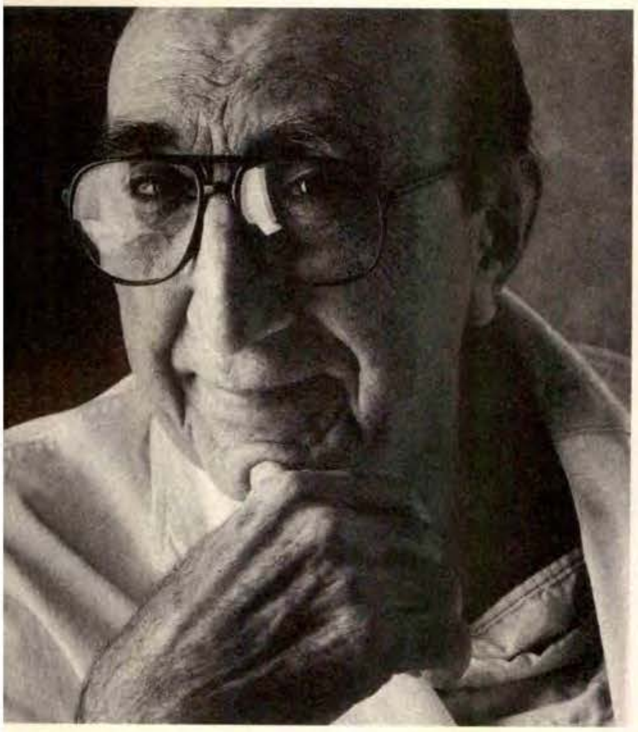
Join Dr. DeBakey.



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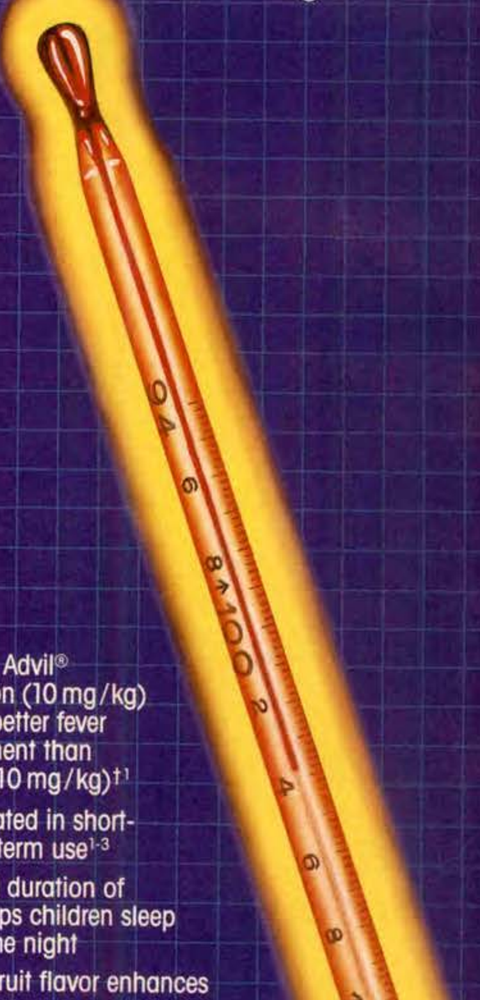

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BRIEF SUMMARY OF PRESCRIBING INFORMATION

INDICATIONS: CHILDREN'S ADVIL® SUSPENSION is indicated for the reduction of fever in patients aged 12 months and older, and for the relief of mild-to-moderate pain in patients aged 12 years and older.

CHILDREN'S ADVIL® SUSPENSION is also indicated for relief of the signs and symptoms of juvenile arthritis, rheumatoid arthritis, and osteoarthritis.

CHILDREN'S ADVIL® SUSPENSION is indicated for the relief of primary dysmenorrhea.

CONTRAINDICATIONS: Patients hypersensitive to ibuprofen or patients with all or part of the syndrome of nasal polyps, angioedema, and bronchospastic reactivity to aspirin or other nonsteroidal anti-inflammatory agents. Anaphylactoid reactions to ibuprofen have occurred in such patients.

WARNINGS: Risk of GI Ulcerations, Bleeding, and Perforation with NSAID Therapy: Physicians should remain alert for ulceration and bleeding in patients treated chronically with NSAIDS even in the absence of previous GI tract symptoms. In patients observed in clinical trials of several months' to two years' duration, symptomatic upper GI ulcers, gross bleeding or perforation appear to occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for one year.

Except for a prior history of serious GI events and other risk factors known to be associated with peptic ulcer disease, no risk factors have been associated with increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less well than other individuals and most spontaneous reports of fatal GI events are in this population.

PRECAUTIONS: General: Because serious GI tract ulceration and bleeding can occur without warning symptoms, physicians should follow chronically treated patients for the signs and symptoms of ulceration and bleeding.

Blurred and/or diminished vision, scotomata, and/or changes in color vision have been reported. If a patient develops such complaints the drug should be discontinued and the patient should have an ophthalmologic examination.

Fluid retention and edema have been reported with ibuprofen; therefore, the drug should be used with caution in patients with a history of cardiac decompensation or hypertension.

Ibuprofen can inhibit platelet aggregation and prolong bleeding time. CHILDREN'S ADVIL® SUSPENSION should be used with caution in persons with intrinsic coagulation defects and those on anticoagulant therapy.

The antipyretic and anti-inflammatory activity of ibuprofen may reduce fever and inflammation, thus diminishing their utility as diagnostic signs in detecting complications of presumed noninfectious, noninflammatory painful conditions.

Small decreases (usually not exceeding one gram) in hemoglobin and hematocrit with an apparent dose response relationship have been observed following chronic administration. If there are no signs of bleeding, it is probably not clinically important.

To avoid exacerbation of disease or adrenal insufficiency, patients on prolonged corticosteroid therapy should have their therapy tapered slowly when CHILDREN'S ADVIL® SUSPENSION is added to the treatment program.

Aseptic meningitis: Aseptic meningitis with fever and coma has been observed on rare occasions in adult patients on ibuprofen therapy. Although it is more likely to occur in patients with systemic lupus erythematosus and related connective tissue diseases, it has been reported in adult patients who do not have underlying chronic disease. If signs or symptoms of meningitis develop in a patient on CHILDREN'S ADVIL® SUSPENSION, the possibility of its being related to ibuprofen should be considered.

Renal Effects: As with other nonsteroidal anti-inflammatory drugs, long-term administration of ibuprofen to animals has resulted in renal papillary necrosis and other abnormal renal pathology. In humans, there have been reports of acute interstitial nephritis with hematuria, proteinuria, and occasionally nephrotic syndrome.

A second form of renal toxicity has been seen in patients with prerenal conditions leading to reduction in renal blood flow or blood volume. In these patients, administration of a nonsteroidal anti-inflammatory drug may cause a dose dependent reduction in prostaglandin formation and precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, and those taking diuretics and the elderly. Those patients at high risk who chronically take CHILDREN'S ADVIL® SUSPENSION should have renal function monitored if they have signs or symptoms of azotemia. Discontinuation of nonsteroidal anti-inflammatory drug therapy is typically followed by recovery to the pretreatment state.

Since ibuprofen is eliminated primarily by the kidneys, patients with significantly impaired renal function should be closely monitored and a reduction in dosage should be anticipated to avoid drug accumulation.

Information for Patients: Physicians may wish to discuss with their patients the potential risks and likely benefits of treatment with CHILDREN'S ADVIL® SUSPENSION.

Laboratory Tests: Meaningful (3 times the upper limit of normal) elevations of SGPT or SGOT (AST) occurred in controlled clinical trials in less than 1% of patients. A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of more severe hepatic reactions while on therapy with ibuprofen. If abnormal liver tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur, CHILDREN'S ADVIL® SUSPENSION should be discontinued.

Diabetes: Each 5 mL of CHILDREN'S ADVIL® SUSPENSION contains 2.5 g of sucrose which should be taken into consideration when treating patients with impaired glucose tolerance. It also contains 350 mg of sorbitol per 5 mL. Although in clinical trials CHILDREN'S ADVIL® SUSPENSION was not associated with more diarrhea than control treatments, should a patient develop diarrhea, the physician may wish to review the patient's dietary intake of sorbitol from other sources.

Drug Interactions: *Coumarin-type Anticoagulants:* Bleeding has been reported when ibuprofen and other nonsteroidal anti-inflammatory agents have been administered to patients on coumarin-type anticoagulants; the physician should be cautious when administering CHILDREN'S ADVIL® SUSPENSION to patients on anticoagulants.

Aspirin: Concurrent use of aspirin is not recommended.

Methotrexate: In vitro studies indicate that ibuprofen could enhance the toxicity of methotrexate. Caution should be used if CHILDREN'S ADVIL® SUSPENSION is administered concomitantly with methotrexate.

H_2 Antagonists: In studies with human volunteers, coadministration of cimetidine or ranitidine with ibuprofen had no substantive effect on ibuprofen serum concentrations.

Furosemide: Ibuprofen can reduce the natriuretic effect of furosemide and thiazides in some patients. During concomitant therapy with CHILDREN'S ADVIL® SUSPENSION, the patient should be observed closely for signs of renal failure as well as to assure diuretic efficacy.

Lithium: Ibuprofen produced an elevation of plasma lithium levels (15%) and a reduction in renal lithium clearance (19%) in a study of 11 normal volunteers during the period of concomitant drug administration. Patients should be observed carefully for signs of lithium toxicity. Read package insert for lithium before its use.

Pregnancy: Administration of ibuprofen is not recommended during pregnancy or for use by nursing mothers.

Infants: Safety and efficacy of CHILDREN'S ADVIL® SUSPENSION in children below the age of 12 months have not been established.

ADVERSE REACTIONS: The most frequent type of adverse reaction occurring with CHILDREN'S ADVIL® SUSPENSION is gastrointestinal. In clinical trials among adults involving chronic administration of ibuprofen, the percentage of patients reporting one or more gastrointestinal complaints ranged from 4% to 16%.

Incidence Greater Than 1% (but less than 3%), Probable Causal Relationship (see PRECAUTIONS): Abdominal cramps or pain, abdominal distress, constipation, diarrhea, epigastric pain,* fullness of the GI tract (bloating and flatulence), heartburn,* indigestion, nausea,* nausea and vomiting; dizziness,* headache, nervousness; pruritus, rash* (including maculopapular type); tinnitus; decreased appetite; edema, fluid retention (generally responds promptly to drug discontinuation).

Precise Incidence Unknown (but less than 1%), Probable Causal Relationship (see PRECAUTIONS): Abnormal liver function tests, gastric or duodenal ulcer with bleeding and/or perforation, gastritis, gastrointestinal hemorrhage, hepatitis, jaundice, melena, pancreatitis; alopecia, erythema multiforme, Stevens-Johnson syndrome, urticaria, vesiculobullous eruptions; aseptic meningitis with fever and coma, confusion, depression, emotional lability, insomnia, somnolence; amblyopia (blurred and/or diminished vision, scotomata and/or changes in color vision), hearing loss; agranulocytosis, aplastic anemia, decreases in hemoglobin and hematocrit, eosinophilia, hemolytic anemia (sometimes Coombs' positive), neutropenia, thrombocytopenia with or without purpura; congestive heart failure in patients with marginal cardiac function, elevated blood pressure, palpitations; anaphylaxis, bronchospasm (see CONTRAINDICATIONS), syndrome of abdominal pain, fever, chills, nausea and vomiting; acute renal failure in patients with pre-existing significantly impaired renal function, azotemia, cystitis, decreased creatinine clearance, hematuria, polyuria; dry eyes and mouth, gingival ulcers, rhinitis.

Precise Incidence Unknown (but less than 1%), Causal Relationship Unknown: Dream abnormalities, hallucinations, paresthesias, pseudotumor cerebri; photoallergic skin reactions, toxic epidermal necrolysis; cataracts, conjunctivitis, diplopia, optic neuritis; bleeding episodes (e.g., epistaxis, menorrhagia); acidosis, gynecomastia, hypoglycemic reactions; arrhythmias (sinus tachycardia, sinus bradycardia); angioedema, Henoch-Schönlein vasculitis, lupus erythematosus syndrome, serum sickness; renal papillary necrosis.

*Reactions occurring in 3% to 9% of adult patients treated with ibuprofen.

OVERDOSAGE: Patients with a history of ingestion of greater than 100 mg/kg should have induced emesis or gastric lavage. Multiple dose oral administration of activated charcoal may be useful. Supportive therapy may include oxygen, respiratory support, and parenteral fluids. Because the drug is acidic and excreted in the urine, administration of sodium bicarbonate and induction of diuresis may be beneficial.

DOSAGE AND ADMINISTRATION: Fever: 5 mg/kg if baseline temperature is 102.5°F or below or 10 mg/kg if baseline temperature is greater than 102.5°F, every 6-8 hours (children); 400 mg every 4-6 hours (adults).

Mild to moderate pain in adults: 400 mg every 4 to 6 hours.

Juvenile Arthritis: 30-40 mg/kg day in 3 or 4 divided doses.

RA and OA: 1200-3200 mg per day in 3 or 4 divided doses.

Dysmenorrhea: 400 mg every 4 hours.

HOW SUPPLIED: 4 and 16 oz. bottles

Caution: Federal law prohibits dispensing without prescription.

References:

1. Watson PD, Galletta G, Braden NJ, Alexander L. Ibuprofen, acetaminophen, and placebo treatment of febrile children. *Clin Pharmacol Ther.* 1989;46:9-17.
2. Independent Clinical Study: Reduction of Fever in Children, Multiple Dose. Data on file, Medical Department, Whitehall Laboratories.
3. Independent Clinical Study: Reduction of Fever in Children, Single Dose. Data on file, Medical Department, Whitehall Laboratories.

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Professional Opportunities

OBERLIN, OHIO — Multi-specialty group seeks BC/BE pediatricians to serve growing patient load. Northern Ohio college town serving drawing area of 275,000. Salary, liberal benefits first year with full shareholder status available thereafter. Send CV to: Dr. VanDyke, 224 West Lorain, Oberlin, OH 44074.

TEXAS — BE/BC pediatrician to join busy, three-pediatrician group in Dallas/Fort Worth Metroplex. Competitive salary, incentives and benefits. Contact: Dan Geppert, MD, 950 North Davis, Arlington, TX 76012. (817) 460-0104.

THIRD PEDIATRICIAN—BRAINERD, MINNESOTA: Join two pediatricians of 22 multi-specialty clinic. No set-up cost. Two hours from Minneapolis. Beautiful lakes and trees; ideal for families. Call collect/write: Curt Nielsen, (218) 828-7105 or (218) 829-4901; Brainerd Medical Center, P.O. Box 524, Brainerd, MN 56401.

BC/BE PEDIATRICIAN to join three pediatricians in university-run ambulatory center with regional hospital and university medical center affiliation, with emphasis on primary care. UMMC is an equal opportunity/affirmative action employer. Location: Southcentral Massachusetts. Appointment in university department of pediatrics. Membership in university group practice. Fringe benefits excellent. Salary negotiable. Reply: David P. Tapscott, MD, 281 East Hartford Avenue, Uxbridge, MA 01569-9658.

FOUR CONGENIAL PEDIATRICIANS seek fifth pediatrician for rapidly expanding practice. This practice is located in an affluent growing community in northern California within a two-hour access to San Francisco and Lake Tahoe. Guaranteed salary for two years with partnership options at the end of the two-year period. Write or call: P.O. Box 787, Lodi, CA 95240. (209) 369-7493.

MANKATO, MINNESOTA—A large multi-specialty group practice is seeking a BC/BE physician to join its five-person pediatric department. Consider practicing in a "micropolitan area"—a smaller city with cosmopolitan qualities. Mankato is ranked ninth as one of the best small cities in the United States to live. First year salary guarantee plus incentive and excellent corporate benefits, along with shareholder status after twelve months. For additional information, please call or send CV to: John Norris, MD, or Roger Greenwald, Executive Vice President, 501 Holly Lane, Mankato, MN 56001. (507) 625-1811.

MAINE: Immediate opportunity for a fourth BC/BE pediatrician with general and/or subspecialty interests to join a multi-specialty group affiliated with a 250-bed regional referral hospital. Enjoy the professional challenge offered in a sophisticated medical community along with the wonderful recreational opportunities and quality of life in Maine. Please send CV to: Richard Marsh, MD, 76 High Street, Suite 203, Lewiston, ME 04240. Or call: (207) 795-2389 and ask for Shannon Tamminen.

EXCEPTIONAL PEDIATRIC PRACTICE opportunity available for a BC/BE pediatrician in a busy midwest multi-specialty clinic. Department currently consists of five pediatricians including services in general pediatrics, pediatric hematology/oncology and neonatolgy. Clinic is attached to a 206-bed hospital with a newly remodeled pediatric ward. It is located in a medically oriented community of 145,000 with excellent schools, two state universities and a private liberal arts college. A very low crime rate. Minnesota's lakes country just a half-hour drive away, thus outdoor activities abound. Excellent fringe benefits and a very competitive starting salary. Please contact: Dakota Clinic, Ltd., Recruiting Division, 1702 South University Drive, Fargo, ND 58103. (701) 280-8520.

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TWO PEDIATRICIANS SEEKING third BC/BE pediatrician to join two site, growing practice. Ideal all season recreational area. Ideal site for young family. Please contact: Tahoe City Pediatrics, P.O. Box 6959, Tahoe City, CA 95730.

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Medical Director

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80 West Avenue, Brockport, NY 14420

CALIFORNIA—Multi-specialty private group practice located in desirable high growth area of southern California seeks general pediatricians, as well as pediatricians with subspecialty of infectious disease, neurology or cardiology. Excellent working conditions, fringe benefits, and congenial staff. Please submit CV to: George Kanaly, PhD, President, Riverside Medical Clinic, 3660 Arlington Avenue, Riverside, CA 92506.

BC/BE PEDIATRICIAN to join two BC private practice pediatricians in upstate New York, Thousand Islands region. Affiliation leading to partnership. Level II NICU, cystic fibrosis center. Stimulating practice with an on-call arrangement with other pediatricians, excellent recreational facilities and schools in a thriving small city with many cultural advantages. A good place to raise children, too. Contact: R.G. Perciaccante, MD, 199 Pratt Street, Watertown, NY 13601.

THE DEPARTMENT OF PEDIATRICS, William Beaumont Hospital is seeking a second pediatric cardiologist to expand our Division of Pediatric Cardiology. William Beaumont Hospital is a 934-bed general hospital with 20 residency programs and a fully accredited training program in pediatrics. The Department of Pediatrics has 23 full-time, 12 part-time and a number of geographic full-time faculty. The inpatient service includes a 52-bed general pediatric ward, a 4-bed PICU (to increase to 6 beds by the summer) and a 30-bed NICU. We are anxious to recruit an individual who is interested in clinical care and teaching but who also has a definite interest in scholarly activity. Contact: M. Jeffrey Maisels, MD, Chairman, Department of Pediatrics, William Beaumont Hospital, 3601 West 13 Mile Road, Royal Oak, MI 48073-6769. (313) 551-0412.

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LARGE MULTI-SPECIALTY GROUP in northern Virginia area needs bilingual pediatrician to replace retiring physician of 40 years. Send CV to: Medical Director, Falls Church Medical Center, 6060 Arlington Boulevard, Falls Church, VA 22044.

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SUFFOLK COUNTY NEW YORK — Seeking general pediatrician BE/BC part-time and vacation coverage to start, with possibility of full-time partnership. Call: (516) 589-6727.

PHILADELPHIA AREA: Three pediatricians seeking BE/BC fourth in growing suburban community. One office practice, minutes from hospital. Full partnership opportunity after two years. Convenient access to Philadelphia, recreational opportunities in nearby Pocono Mountains and/or New Jersey Beaches. Send CV to: Stephen R. Gershenson, MD, 587 Bethlehem Pike, Montgomeryville, PA 18936.

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Eleven member pediatric division of multi-specialty group practice serving prepaid and fee-for-service patients looking for twelfth pediatrician to do general pediatrics. In addition to full-time position, willing to consider part-time or job-share opportunities. Subspecialty interests possible. University affiliation encouraged. Competitive salary and benefits. Located in attractive metropolitan area with many cultural and recreational advantages.

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NEONATOLOGIST to join five-member BC/BE group in a Level III perinatal center with academic affiliation. For further information, contact: B.T. Bloom, MD, 550 North Hillside, Wichita, KS 67214. (316) 688-2360.

Professional Opportunities

PENNSYLVANIA—Small multi-specialty group in Lycoming County needs one or two BE/BC pediatricians. $85,000-$130,000 net potential plus benefits and malpractice insurance. Built in referrals. Premium schools. Contact: Perry Robinson, Cejka & Co., 222 South Central, Suite 700, St. Louis, MO 63105. (800) 765-3055.

Position Available

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The American Board of Pediatrics has appointed a search committee to select a President of the Board with service to begin in 1991. The person selected for this full-time position will serve as the Chief Executive Officer of the Board.

We seek a distinguished, certified pediatrician who is an experienced educator and who is familiar with the procedures and operations of the American Board of Pediatrics.

Send nominations with a curriculum vitae to the Chairman of the Search Committee, Laurence Finberg, MD, at 111 Silver Cedar Court, Chapel Hill, NC 27514.

PEDIATRICIANS NEEDED: BE/BC full-time, needed to join Carle Clinic — Danville, Illinois; a 40,000+ rural, industrial community on the scenic Illinois/Indiana border, draws patients from both states. This 15 physician group is part of a 210 physician, multi-specialty, group practice in central Illinois; liberal fringe benefits including liability coverage, and competitive salary leading to equal ownership. Write, including CV to: Robert C. Parker, Jr., MD, Assistant to the Chief Executive Officer, Carle Clinic Association, 602 West University, Urbana, IL 61801. Or call collect at (217) 337-3417, FAX (217) 337-3163.

ADOLESCENT MEDICINE

Unique opportunity for academic adolescent medicine specialist. The Department of Pediatrics, Northwestern University Medical School is seeking a Head of Adolescent Medicine for its patient care and educational programs at the Evanston Hospital and the Children's Memorial Hospital. This individual will spend the majority of time at The Evanston Hospital serving the needs of adolescents, including a Child and Adolescent Center with over 2,000 adolescent visits annually. Participation in the University Student Health Service is available.

This position will have responsibility for a teaching curriculum in adolescent medicine for 60+ pediatric residents from the Residency Training Program of Children's Memorial Hospital. Ample time will be provided for clinical research. Interest in sports medicine is desirable. Board-eligibility/-certification in pediatrics and completion of an adolescent medicine fellowship are required. Faculty rank and salary will be commensurate with a candidate's experience.

Interested candidates should send curriculum vitae and supporting documents to:

David Ingall, MD, Chairman
Department of Pediatrics

THE EVANSTON HOSPITAL
2650 Ridge Avenue, Evanston, IL 60201

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The University of South Dakota School of Medicine currently has openings for BE/BC pediatric subspecialties.

These are full-time academic positions ideally suited for the clinician scholar who wishes to develop and guide a program which will have a significant impact on the health care of children. Although our program is heavily slanted toward medical student education and patient care, the department encourages and provides ample resources for clinical and laboratory research.

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for existing practice with three other board-certified pediatricians (vacancy due to retiring physician). Our 33-physician, multi-specialty clinic is located 115 miles from Chicago, 50 miles from Rockford and is adjacent to a 135-bed, acute care hospital, with a Level II Nursery having state-of-the-art equipment.

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This positions offers an attractive call schedule of every fourth night and fourth weekend. Phone calls during the daytime are covered by well-trained RNs to free up time for clinical practicing pediatrics without interruption. Excellent first year guaranteed salary with incentives; partnership opportunity after one year.

Send CV to: E. Scott Bowmer, Administrator,

Sterling Rock Falls Clinic, Ltd.

101 E. Miller Road, Sterling, IL 61081

Professional Opportunities

FLORIDA — Energetic, BC/BE pediatrician wanted to join large, nationally respected pediatric practice in Broward County, Florida, part-/full-time. Reply to: Peter Shulman, MD, Pediatric Associates, PA, 350 NW 70th Avenue, Suite 350A, Plantation, FL 33317. (305) 581-4400.

Faculty Positions

SOUTHEAST USA — academic pediatrician: Teach medical students and family practice residents. Direct patient care and clinical research interests required. Alabama state medical license required. Should be board-eligible or board-certified. The University of Alabama is an equal opportunity affirmative action employer. Send inquiries with CV to: David C. Hefelfinger, MD, Department of Pediatrics, 700 University Boulevard East, Tuscaloosa, AL 35401. (205) 348-1304.

PEDIATRICIAN — PRIMARY CARE (Washington, DC Greater Metropolitan Area): Full-time faculty pediatrician needed to share in clinical practice of university-based HMO, located in suburban Alexandria, Virginia. Faculty appointment (non-tenure) in innovative department of primary, community and preventive medicine. Teacher/role model for medical students, residents. BC/BE; academic/ambulatory experience preferred. Position available July 1, 1991. Applications accepted until position is filled. Review of applications will commence April 1, 1991. Send CV with cover letter to: Megan Kim, ACC, Room G-203, Pediatric Division, Department of Health Care Sciences, George Washington University, 2150 Pennsylvania Avenue, NW, Washington, DC 20037. The George Washington University is an equal opportunity employer.

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Faculty Positions

AMBULATORY PEDIATRICS — Nonspecified: The Department of Pediatrics, University of Illinois College of Medicine at Rockford seeks a BC/BE pediatrician for an academic position in an ambulatory setting. The Community Health Center program is a longitudinal, comprehensive experience in primary care medicine. Each center is staffed by full-time faculty. Responsibilities include supervision of medical students in an ambulatory setting, direct patient care, quality assurance activities and clinical research. For earliest consideration please reply by: May 1, 1991. Reply with CV to: D.H. Wortmann, MD, Chairman, Department of Pediatrics, UICOM-R, 1400 Charles Street, Rockford, IL 61104. UICOM-R is an equal opportunity/affirmative action employer.

WYOMING — University of Wyoming Family Practice Residency-Casper is seeking an experienced, clinically oriented, board-certified pediatrician to be the pediatric coordinator of an 8-8-8 family practice residency program. Level II Nursery skills are a must. 60% teaching, 20% direct patient care, 20% research. This is a tenure track position. University approval will be required prior to filling this position. Come join us in beautiful Wyoming! Contact: Dr. David Driggers, Director, University of Wyoming Family Practice Residency, 1522 East "A" Street, Casper, WY 82601. (307) 266-3076. The University of Wyoming is an affirmative action/EOE.

PEDIATRIC CARDIOLOGY — Assistant/Associate Professor: The Department of Pediatrics, Univesity of Illinois College of Medicine at Rockford seeks candidates for academically based full-time Associate Director for Division of Pediatric Cardiology. Position includes commitment to high quality of patient care, medical student/house staff teaching, and protected time for research. Must be BC/BE and eligible for licensure in Illinois. For earliest consideration please reply by May 1, 1991. Reply with CV to: D.H. Wortmann, MD, Chairman, Department of Pediatrics, UICOM-R, 1400 Charles Street, Rockford, IL 61104. UICOM-R is a equal opportunity/affirmative action employer.

Pediatric Emergency Medicine Physicians

The Department of Pediatrics at Boston City Hospital/Boston University School of Medicine is seeking academically oriented pediatric emergency room physicians.

The Pediatric Emergency Department sees approximately 24,000 visits annually in a newly constructed Pediatric Emergency Room. Boston City Hospital is a Level 1 Trauma Center with an active teaching and research component.

As a member of a staff of full time attendings, the candidate will participate in direct patient care and supervision of house staff and pediatric emergency medicine fellows. Opportunity to develop individual and collaborative research project is encouraged.

The candidate must be BC/BE in pediatrics with pediatric emergency medicine fellowship training or equivalent experience. Competitive salary and benefits.

Please respond with curriculum vitae to: Robert J. Vinci, M.D., Director of Pediatric Emergency Medicine, Talbot Building, Suite 106, Boston City Hospital, 818 Harrison Avenue, Boston, MA 02118. AA/EOE.

Boston University Medical Campus

CHAIR

DEPARTMENT OF PEDIATRICS AND ADOLESCENT MEDICINE

Nominations and applications are invited for the chair of the Department of Pediatrics and Adolescent Medicine, St. Louis University School of Medicine. The department provides a full range of clinical services in pediatrics at the Cardinal Glennon Children's Hospital. The 190 bed hospital is located adjacent to the School of Medicine and the St. Louis University Hospital. The department is responsible for teaching medical students, training residents and fellows, and carrying on a productive program of research. The hospital in conjunction with the School of Medicine has established the Pediatric Research Institute to further the research endeavors of the department.

Nominations and applications should be addressed to David Lagunoff, M.D., Chairman of the Search Committee, 301 Caroline, St. Louis University School of Medicine, 1402 South Grand Boulevard, St. Louis, MO 63104. (314) 577-8108

St. Louis University Medical Center

Cardinal Glennon Children's Hospital

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Faculty Positions

THE DEPARTMENT OF PEDIATRICS of The Ohio State University located at Children's Hospital in Columbus, Ohio, is seeking full-time academically-oriented pediatric emergency medicine physicians at the assistant to full professor levels. Children's Hospital's emergency room currently sees over 65,000 patients per year. The facility is the region's pediatric trauma center. Applicants should be board-certified/-eligible in pediatrics with completed fellowship training and/or experience in pediatric emergency medicine. Responsibilities include direct care of pediatric patients; teaching and supervision of pediatric emergency medicine fellows, medical students, and residents in pediatrics, emergency medicine and family practice. Excellent opportunities for research. Competitive salary and benefits. Send curriculum vitae to: Gary Smith, MD, Dr. PH, Director of Emergency Medical Services, Children's Hospital, 700 Children's Drive, Columbus, OH 43205. The Ohio State University is an equal opportunity/affirmative action employer.

THE OHIO STATE UNIVERSITY Department of Pediatrics is seeking a board-certified/board-eligible neonatologist. Responsibilities include patient care, teaching, and research in an academically oriented children's hospital. The position is a full-time academic position. Competitive salary and benefits. Applicants should send curriculum vitae to: James A. Menke, MD, Associate Professor, Department of Pediatrics, The Ohio State University, 700 Children's Drive, Columbus, OH 43205. The Ohio State University is an affirmative action/equal opportunity employer.

DIVISION OF HEMATOLOGY, Department of Pediatrics, University of Pennsylvania School of Medicine is seeking MD or MD/PhD for appointment at Assistant Professor level. Candidate should have experience in biophysics and molecular biology of white cells and other hematopoietic cells, as well as experience in clinical and basic research regarding growth factors. Send CV to: Alan Cohen, MD, Acting Director, Division of Hematology, The Children's Hospital of Philadelphia, 34th Street and Civic Center Boulevard, Philadelphia, PA 19104. The University of Pennsylvania is an equal opportunity/affirmative action employer.

Directors Wanted

NEONATAL CO-DIRECTOR sought: BC/BE neonatologist for fee-for-service private practice in Level II, 18-bed nursery with 1,800 plus deliveries. Clinical, administrative and minimal teaching responsibilities (medical school and family practice residency). 150-bed, referral hospital located in Illinois university city. Great educational and recreational opportunities. Call Georgetta: (800) 328-3666.

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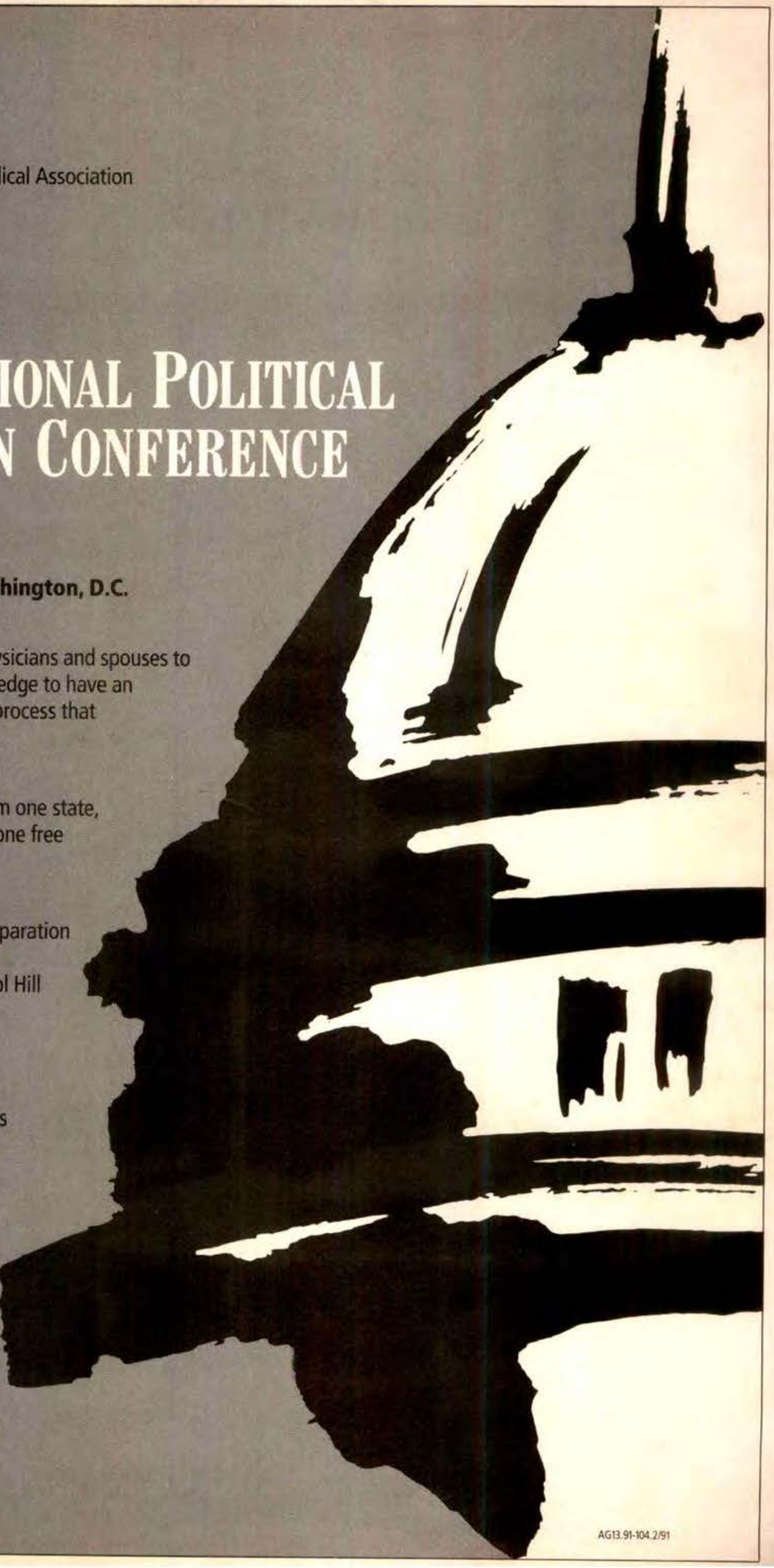

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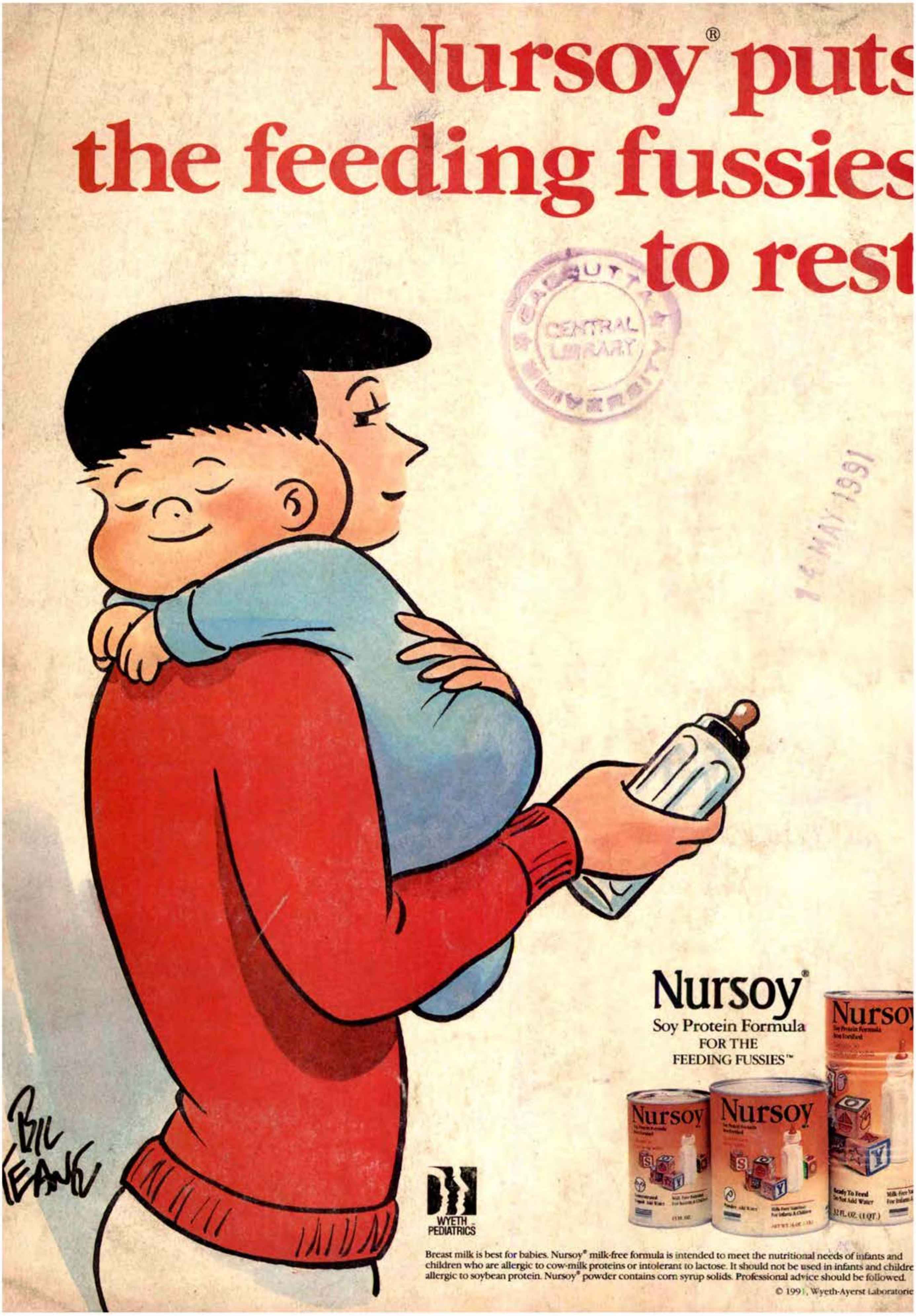

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MAY 1991

Far From the Ideal: Poor Children in the US

Volume 145, Number 5

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EDITORIALS

Far From the Ideal: The Plight of Poor Children in the United States 489
Vincent A. Fulginiti, MD, New Orleans, La

Youth Alienation as an Emerging Pediatric Health Care Issue 491
James A. Farrow, MD, Seattle, Wash

THE PEDIATRIC FORUM

New Initiatives in Adolescent Health Promotion 495
Arthur B. Elster, MD, Chicago, Ill

ARTICLES

Redoing the Health Care Quilt: Patches or Whole Cloth? 499
William W. Cleveland, MD, Miami, Fla

A Regional Pediatric Approach to the Epidemic of Social Ills Within Our Cities 505
Waldo E. Nelson, MD, Philadelphia, Pa

Poverty and the Health of American Children: Implications for Academic Pediatrics 507
Richard B. Johnston, Jr, MD, Philadelphia, Pa

Improving Health Care Provision to Neonates in the United States 510
Mildred T. Stahlman, MD, Nashville, Tenn

Child Abuse and Neglect: Critical First Steps in Response to a National Emergency: The Report of the US Advisory Board on Child Abuse and Neglect 513
Richard D. Krugman, MD, Denver, Colo

Continued on page 483.

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Children in and of the Streets: Health, Social Policy, and the Homeless Young 516
James D. Wright, PhD, New Orleans, La

A Survey of the Health of Homeless Children in Philadelphia Shelters 520
Ruth M. Parker, MD, Atlanta, Ga; Leslie A. Rescorla, PhD, Bryn Mawr, Pa;
Jonathan A. Finkelstein, MD, Boston, Mass;
Nathaniel Barnes, MD, Durham, NC;
John H. Holmes, MS, Paul D. Stolley, MD, MPH, Philadelphia, Pa

Pediatric Acquired Immunodeficiency Syndrome, Poverty, and National Priorities 527
Margaret C. Heagarty, MD, New York, NY

Pediatric Human Immunodeficiency Virus Infection and the Acquired Immunodeficiency Syndrome: A Health Care Crisis of Children and Families 529
Russell B. Van Dyke, MD, New Orleans, La

The American Academy of Pediatrics Response to the Growing Health Needs of Children 536
James E. Strain, MD, Elk Grove Village, Ill

The Growing Neglect of American Children 540
Harold M. Maurer, MD, Salt Lake City, Utah

The Challenge of Care for the Poor Child: The Research Agenda 542
Steve Kohl, MD, San Francisco, Calif

Serving the Underserved: Impact on Resident Education 544
Carol D. Berkowitz, MD, McLean, Va

The Challenge of Care for the Poor and Underserved in the United States: An American College of Obstetricians and Gynecologists Perspective on Access to Care for Underserved Women 546
Ezra C. Davidson, Jr, MD; Charles E. Gibbs, MD;
Janet Chapin, MPH, Washington, DC

Poverty and Cardiac Disease in Children 550
Hugh D. Allen, MD; Kathryn A. Taubert, PhD;
Richard J. Deckelbaum, MD; David Driscoll, MD;
Ann Dunnigan, MD; Samuel S. Gidding, MD;
Paul Herndon, MD; Rae-Ellen W. Kavey, MD;
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Continued on page 487.

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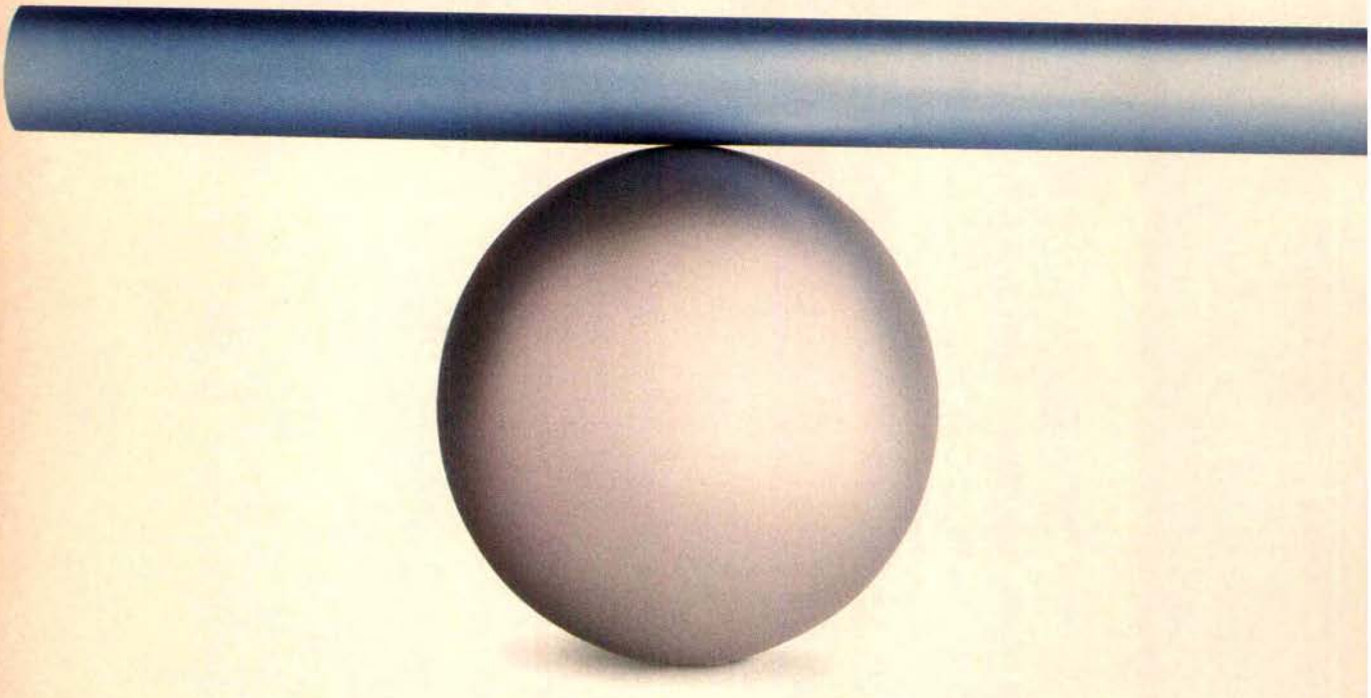

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CONTRAINDICATIONS: PediaProfen should not be used in patients who have previously exhibited hypersensitivity to ibuprofen, or in individuals with all or part of the syndrome of nasal polyps, angioedema and bronchospastic reactivity to aspirin or other nonsteroidal anti-inflammatory agents. Anaphylactoid reactions have occurred in such patients.

WARNINGS: Risk of GI Ulceration, Bleeding and Perforation with NSAID Therapy. Serious gastrointestinal toxicity such as bleeding, ulceration, and perforation, can occur at any time, with or without warning symptoms, in patients treated chronically with NSAID therapy. Although minor upper gastrointestinal problems, such as dyspepsia, are common, usually developing early in therapy, physicians should remain alert for ulceration and bleeding in patients treated chronically with NSAIDs even in the absence of previous GI tract symptoms. In patients observed in clinical trials of several months to two years duration, symptomatic upper GI ulcers, gross bleeding or perforation appear to occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for one year. Physicians should inform patients about the signs and/or symptoms of serious GI toxicity and what steps to take if they occur.

Studies to date have not identified any subset of patients not at risk of developing peptic ulceration and bleeding. Except for a prior history of serious GI events and other risk factors known to be associated with peptic ulcer disease, such as alcoholism, smoking, etc., no risk factors (e.g., age, sex) have been associated with increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less well than other individuals and most spontaneous reports of fatal GI events are in this population. Studies to date are inconclusive concerning the relative risk of various NSAIDs in causing such reactions. High doses of any NSAID probably carry a greater risk of these reactions, although controlled clinical trials showing this do not exist in most cases. In considering the use of relatively large doses (within the recommended dosage range), sufficient benefit should be anticipated to offset the potential increased risk of GI toxicity.

PRECAUTIONS: General: Blurred and/or diminished vision, scotomata, and/or changes in color vision have been reported. If a patient develops such complaints while receiving **PediaProfen**, the drug should be discontinued and the patient should have an ophthalmologic examination which includes central visual fields and color vision testing.

Fluid retention and edema have been reported in association with ibuprofen; therefore, the drug should be used with caution in patients with a history of cardiac decompensation or hypertension.

PediaProfen, like other nonsteroidal anti-inflammatory agents, can inhibit platelet aggregation, but the effect is quantitatively less and of shorter duration than that seen with aspirin. Ibuprofen has been shown to prolong bleeding time (but within the normal range) in normal subjects. Because this prolonged bleeding effect may be exaggerated in patients with underlying hemostatic defects, **PediaProfen** should be used with caution in persons with intrinsic coagulation defects and those on anticoagulant therapy.

Patients on **PediaProfen** should report to their physicians signs or symptoms of gastrointestinal ulceration or bleeding, blurred vision or other eye symptoms, skin rash, weight gain, or edema.

In order to avoid exacerbation of disease of adrenal insufficiency, patients who have been on prolonged corticosteroid therapy should have their therapy tapered slowly rather than discontinued abruptly when ibuprofen is added to the treatment program.

The antipyretic and anti-inflammatory activity of **PediaProfen** may reduce fever and inflammation, thus diminishing their utility as diagnostic signs in detecting complications of presumed noninfectious, noninflammatory painful conditions.

Since ibuprofen is eliminated primarily by the kidney, patients with significantly impaired renal function should be closely monitored and a reduction in dosage should be anticipated to avoid drug accumulation. Prospective studies on the safety of ibuprofen in patients with chronic renal failure have not been conducted.

Safety and efficacy of **PediaProfen** in children below the age of 6 months has not been established.

Pregnancy: Reproductive studies conducted in rats and rabbits at doses somewhat less than the maximal clinical dose did not demonstrate evidence of developmental abnormalities. However, animal reproduction studies are not always predictive of human response. As there are no adequate and well-controlled studies in pregnant women, this drug should be used during pregnancy only if clearly needed. Because of the known effects of nonsteroidal anti-inflammatory drugs on the fetal cardiovascular system (closure of ductus arteriosus), use during late pregnancy should be avoided. As with other drugs known to inhibit prostaglandin synthesis, an increased incidence of dystocia and delayed parturition occurred in rats. Administration of **PediaProfen** is not recommended during pregnancy.

ADVERSE REACTIONS: The most frequent type of adverse reaction occurring with ibuprofen is gastrointestinal. In controlled clinical trials, the percentage of adult patients reporting one or more gastrointestinal complaints ranged from 4% to 16%.

Adverse reactions occurring in 3% to 9% of patients treated with ibuprofen: nausea, epigastric pain, heartburn, dizziness, rash. *Adverse reactions occurring in 1% to 3% of patients:* diarrhea, abdominal distress, nausea and vomiting, indigestion, constipation, abdominal cramps or pain, fullness of GI tract, headache, nervousness, pruritus, tinnitus, decreased appetite, edema, fluid retention (generally responds promptly to drug discontinuation). Still other reactions (less than 1 in 100) have been reported, and are detailed in the full summary of prescribing information.

DOSAGE AND ADMINISTRATION: Shake well prior to administration.

Fever Reduction in Children 6 months to 12 years of age: Dosage should be adjusted on the basis of the initial temperature level (See CLINICAL PHARMACOLOGY for a description of the controlled clinical trial results). The recommended dose is 5 mg/kg if the baseline temperature is less than 102.5°F or 10 mg/kg if the baseline temperature is greater than 102.5°F. The duration of fever reduction is generally 6-8 hours and is longer with the higher dose. The recommended maximum daily dose is 40 mg/kg.

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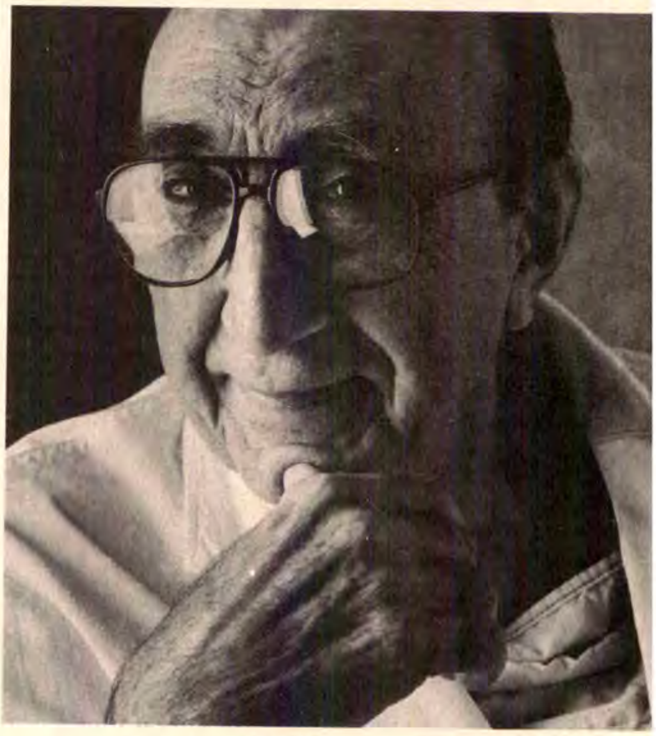

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AMERICAN JOURNAL OF DISEASES OF CHILDREN

The Challenge of Caring for Indigent Children With Rheumatologic Diseases 554
Michael L. Miller, MD, San Antonio, Tex;
Patience H. White, MD, Washington, DC

What Will It Take to Fully Protect All American Children With Vaccines? 559
Alan R. Hinman, MD, MPH, Atlanta, Ga

Improving Health Care for Underserved Infants, Children, and Adolescents: The Robert Wood Johnson Foundation's Experience 565
Michael P. Beachler, Princeton, NJ

Care of the Poor and Underserved in America: Older Adolescents: A Group at Special Risk 569
Robert J. Haggerty, MD, New York, NY

Health Care for Pregnant Women and Young Children 572
Richard E. Behrman, MD, Carol S. Larson, JD, Los Altos, Calif

Children's Services in an Era of Budget Deficits 575
Barbara B. Blum, Susan Blank, New York, NY

The Caring Program for Children: The Michigan Experience 579
Marianne Udow, MHSA; Vernon K. Smith, PhD;
Margaret H. Mason, MHSA, Detroit, Mich

CORRECTION

Lipoprotein Profiles in Hypercholesterolemic Children 515
Richard E. Garcia, MD, Douglas S. Moodie, MD, Cleveland, Ohio

BOOK REVIEWS

Seizures and Epilepsy in Childhood: A Guide for Parents 539
Peggy C. Ferry, MD, Tucson, Ariz

Difficult Diagnosis in Pediatrics 541
Robert Kamei, MD, San Francisco, Calif

REGULAR DEPARTMENTS

Instructions for Authors 488

Classified Advertising 583

Index to Advertisers 588

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Far From the Ideal

The Plight of Poor Children in the United States

The child on the cover of this month's issue of *AJDC* was visualized as an ideal by an unknown painter in colonial times. The child is beautiful, well nourished, placid, and obviously well cared for. This is the ideal that many think of when asked to picture our aspirations for our children. Unfortunately, in the United States today, we fall far short of providing that ideal for millions of infants, children, adolescents, and young adults. This issue of *AJDC* is devoted to exploring the dimensions of and reasons for the problems as well as offering potential corrective actions that might be applied to the plight of our underserved or unserved youth. We embarked on this issue as part of the family of American Medical Association journals' efforts to highlight what has become a national disgrace: 47 000 000 or more ndividuals are neglected at a time when many in the United States enoy the highest level of health in the history of humanity. We hope that our readers will learn of this awful circumstance and, to the extent possible, take action locally, regionally, and nationally to effect some of our authors' remedial suggestions.

We embarked on the development of this issue by inviting commentares from individual leaders in pediatrics, from spokespersons for our professional societies, and from diectors of our major foundations and organizations that offer support and unding for programs that benefit hildren. We may not have invited all who could participate to do so, and ome of those invited did not repond. However, a cross section of ndividuals did respond and covered ll of the issues one might think of when considering the extent of the problems. We thank those who did so nd offer our readers their comments.

We also received unsolicited manuscripts whose themes were consistent with the major intent of this issue of the journal. We have included those that seemed pertinent in our "Pediatric Forum" and "Original Article" departments. They form a unified whole with the solicited articles.

To highlight some of the generic issues common to many of the thematic articles in this issue, I offer the following observations:

1. The dimension of the problem is enormous. More than 37 million children live in poverty, an additional 10 million have no health insurance, and an unknown number have inadequate health care. Many of these children receive no care at all or only urgent care, in fragmented fashion, often for late-stage or even end-stage disease. For most of this population, preventive services are nonexistent or inaccessible because of poverty, lack of knowledge, or failure of insurance programs to cover preventive services. The legacy of this neglect will be felt for many generations to come if we do not take urgent and emphatic action. We will have a host of unhealthy adults and lose significant numbers of otherwise contributing members of society. We also will lose the diversity of ethnicity that is desirable in our leadership ranks in all areas of society.

2. The reasons for the lack of medical care are legion; the most often cited in the reports in this issue are financial. Our national economic plight, with high national debt, diversion of funds from social programs to other areas of the budget, redistribution of federal support to states and cities (which cannot supply the redistributed services because of their own economic difficulties), and now, the added potential cost of the conflict in the Persian Gulf area, has resulted in inadequate resources for health-related programs. Non–health care social programs suffer from the same maldistribution of resources. As a result, poverty increases, homelessness skyrockets, and the causes of ill health multiply.

Apart from financial considerations, which are a major part of the problem, societal issues combine to deny adequate health care. For reasons that are unclear, children lack a voice in the halls of power, especially compared with other segments of our population, such as the elderly. Society voices the bland sentiment that children are our "most valuable resource" but does not protest when we do not ensure that this most valuable resource has an opportunity for a healthy life. In recent years, the American Academy of Pediatrics has become a voice heard in Congress and in other settings as an advocate for children and their needs. However, this is a relatively recent phenomenon and has not yet reached the magnitude of advocacy for the elderly. Strain's contribution[1] in this issue outlines the approach taken by the academy to influence adequate health planning for our youth.

Children whose parents have habits that result in congenital drug addiction and/or congenital infection with human immunodeficiency or hepatitis viruses receive a legacy over which they have no control. They are innocent victims of society's inability or lack of commitment to deal with these problems of their parents. Several contributors to this issue focus on the resulting ill health attendant on such neglect.

Another contributing factor is what I term the *disease of the month* mentality prevalent in allocating money to health programs. Many governmental and private programs are funded to satisfy the demands of potent advocacy groups for specific diseases. In other instances, a powerful individual, sometimes for personal reasons, supports a specific disease program. Added to this set of factors is advocacy by specific professional societies, each with its own agenda. Although this kind of advocacy, and subsequent funding, results in good care for some segments of the population, such specialized program development often substitutes for a more coherent, more widely applicable medical or preventive care program that could offer greater benefit for a larger proportion of our population. Cleveland[2] elaborates on this theme in his discussion of the "patchwork" vs "quilt" approach to health care.

Society also has neglected our adolescents, whose rising pregnancy rate results in increased prematurity, inadequate parenting, and reinforcement of poverty, ill health, and dangerous life-styles. A number of our authors have highlighted this critical area.

Members of society "bill and coo" over the infant born to parents in good financial condition, but ignore the minority infant in the intensive care unit who struggles first to exist and then to remain functionally intact. Members of society bemoan our high neonatal and infant mortality rates compared with other developed societies but do little to advocate for the resources that are needed to prevent prematurity and manage conditions leading to excessive morbidity and mortality. Commentators in this issue highlight the toll resulting from such inattention to this critical period in life.

3. Potential corrective actions are outlined for each of the areas covered by the articles in this issue. Some are relatively simple to accomplish, requiring some rededication of effort but little extra funding. Others will require considerable funding and a change in our national priorities. However, most readers reach the overwhelming conclusion that we need a fundamental change in our national commitment. We need to behave as if children are really our most valuable resource and our future. Therefore, mothers must be afforded healthy pregnancies so newborns will be healthy and born at term, and children must be freed from preventable childhood diseases. They must enjoy normal growth and development and receive an effective education, which should include knowledge and skills needed to understand health and to effect behavioral changes that lead to prevention and avoidance of disease. Parents and children must also learn how to gain early and effective access to the health care system.

Rather than be discouraged by the scope of the problem, we suggest that readers use the data and recommendations in this issue to take action in individual practices, professional societies, medical schools, residency programs, and communities to become advocates for change at all levels of government. We need to take such actions now, not later. We can solve these problems with a unified will, but it will take a society that is willing to move itself from complacency to a new position of concern and action. We at *AJDC* believe we have taken a first step by presenting the articles in this issue; each of you can now take the necessary steps in the immediate future.

Vincent A. Fulginiti, MD
Editor, *AJDC*
Dean's Office
Tulane University School
of Medicine
1430 Tulane Ave
New Orleans, LA 70112

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Youth Alienation as an Emerging Pediatric Health Care Issue

Many young people have withdrawn or are separated from the values of their society or family. These are our alienated youth. The number of adolescents without a defined role in modern society is growing.[1] The inability of children to find a meaningful and productive place in American society both contributes to and stems from the "new morbidities of youth," including early sexual activity, drug abuse, school failure, family violence, and the like. A dearth of descriptive information exists on this growing population of alienated adolescents, which includes runaways, teenaged prostitutes, street youth, school dropouts, and delinquents, to name but a few.[2] The problem of alienation during adolescence, which began to be of major sociological concern in the 1960s, today constitutes an emergent area of study for health care professionals.

These young people, because of forced or adopted destructive lifestyles, are exposed more than most youth to both physical and emotional illness and to the untoward consequences of early sexual activity, such as pregnancy and exposure to sexually transmitted diseases, including acquired immunodeficiency syndrome.[3] For example, more than half of all homeless adolescent girls become pregnant while on the streets.[4] Likewise, those who live in inner cities and come from the underclass often migrate to environments where violence and bodily injury occur frequently and gang affiliation becomes inevitable. Opportunities therefore to reclaim these "wayward" youth become more difficult if the pattern of alienation is not recognized early.

While the largest group of alienated young people are of ethnic minority backgrounds, generally from the lower socioeconomic strata, their values and attitudes often remain similar to those of their families and culture.[5] Equally alarming is the increasing number of alienated youth who come from middle-class America: runaways, street youth, punk rockers, delinquents, and school dropouts. Many of these youth are in conflict with their families and middle-class institutions because of a rejection of parental values or an attraction to subcultures that are perceived as more akin to themselves and supportive than their families, schools, or everyday peers. Few of these young people are running away from unfortunate or abusive home lives. Yet another group, the so-called throwaway kids, are asked by their families to leave at a young age. Many of these young people are depressed, have limited educations, and are unemployable; thus, they are unlikely to become productive citizens.

The number of alienated youth in America is large. By conservative estimates, more than 1 million youth run away from home each year.[6] Nationwide, more than 25% of all high school students drop out.[7] More than ½ million adolescents are incarcerated in secure facilities each year.[8] Estimates of the number of homeless teenagers on the street are rough at best. It is impossible to obtain accurate data for these large groups, in part because they do not congregate and many return home and to the streets in an unpredictable fashion. At a very young age these adolescents begin having difficulties fitting in, and the likelihood is high that as young adults they will have even more difficulty becoming independent, productive members of society.

Alienated youth are frequently outside the health care system and tend to remain there unless efforts are made to identify them and develop health services that are acceptable to them. The adoption of destructive life-styles by many of these youth contributes heavily to physical and psychological morbidity and to an alarmingly high mortality rate. Because health care is one of the more acceptable areas of interaction with these adolescents, some members of the health care community have been remarkably creative in their outreach and development of health services. A few model adolescent and young adult "street clinics" offer free, comprehensive health care services to this population. Those clinics that are affiliated with medical schools and specifically adolescent medicine provide many opportunities for pediatricians in training or in practice to be involved.

Even when the pediatrician is not involved in the regular care of homeless and alienated adolescents, motivated clinicians are aware of specialized resources in the community for this group. These resources include shelter services, free or easy-access adolescent clinics, counseling or support groups for gay and lesbian youth, adolescent chemical dependency treatment programs, and alternative schools. However, few cities have successfully developed comprehensive service programs and many of these components of care may not be available, or homeless and "emancipated" minors may not be eligible. Job training programs for runaways, juveniles involved in prostitution, and older street youth are becoming more prevalent in cities, but often cannot meet the great demand for services.[9]

Perhaps even more important is the pediatrician's advocacy role in promoting healthier outcomes before the alienation process progresses in adolescence. Pediatricians frequently see children who are beginning to have problems associated with alienation. Alienation is often preceded by childhood emotional trauma and ongoing stress. Repeated stress-related illness, school absences, new behaviors stemming from depression, irritability, or anxiety may ultimately escalate into a situation during early adolescence that makes reconciliation between children and parents more difficult.

The pediatrician should take every opportunity during the earlier years to explore family relationship concerns and problem behaviors with children and parents. For older children and younger adolescents, the general psychosocial history should be discussed with the young person in a confidential setting. The degree to which the young person has begun to separate himself or herself from activities normal for his or her age should be assessed. Family relationships, leisure activities, the patient's association with a deviant peer group, school attendance and performance, alcohol and drug experience, sexual behaviors and concerns about sexual identity, and symptoms of depression and withdrawal are important areas to explore. Alienated youth have usually encountered problems in most of these areas.

Early intervention and referral, orchestrated by a caring pediatrician who recognizes the early signs of alienation, who has developed empathy for the experience of these young people and their families, and who knows community resources can be of great help in averting future adoption of destructive behaviors and lifestyles.

While physicians as individual practitioners have a responsibility for providing anticipatory guidance to families and caring for these youth in clinical settings, a great deal more regional and national attention should be given to this large portion of American youth. Physicians can take an active role in developing community resources to meet the needs of alienated youth. They can volunteer to serve on agency boards, committees, and groups to provide the expertise and understanding of a physician who is familiar with these youth and their health issues. The health perspective is important. We are at great risk of losing through apathy, illness, injury, and death many children who have a great deal more potential for productive adult lives than we often recognize.

James A. Farrow, MD
Division of Adolescent
Medicine
University of Washington
WJ-10
Seattle, WA 98105

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G.U. System: Urinary frequency, difficult urination.

G.I. System: Epigastric discomfort, anorexia, nausea, vomiting, diarrhea, constipation.

Respiratory System: Tightness of chest and wheezing, shortness of breath.

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Toxic Doses: Data suggest that individuals may respond in an unexpected manner to apparently small amounts of a particular drug. A 2 1/2-year-old child survived the ingestion of 21 mg/kg of dextromethorphan exhibiting only ataxia, drowsiness, and fever, but seizures have been reported in 2 children following the ingestion of 13-17 mg/kg. Another 2 1/2-year-old child survived a dose of 300-900 mg of brompheniramine. The toxic dose of pseudoephedrine should be less than that of ephedrine, which is estimated to be 50 mg/kg.

Treatment: Induce emesis if patient is alert and is seen prior to 6 hours following ingestion. Precautions against aspiration must be taken, especially in infants and small children. Gastric lavage may be carried out, although in some instances tracheostomy may be necessary prior to lavage. Naloxone hydrochloride 0.005 mg/kg intravenously may be of value in reversing the CNS depression that may occur from an overdose of dextromethorphan. CNS stimulants may counter CNS depression. Should CNS hyperactivity or convulsive seizures occur, intravenous short-acting barbiturates may be indicated. Hypertensive responses and/or tachycardia should be treated appropriately. Oxygen, intravenous fluids, and other supportive measures should be employed as indicated.

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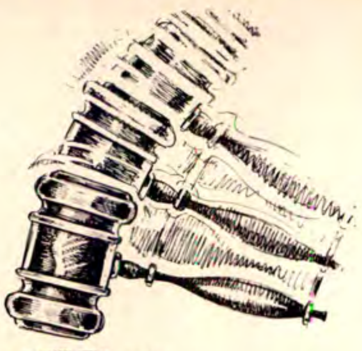

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New Initiatives in Adolescent Health Promotion

Sir.—Health issues facing adolescents have changed dramatically over the last several decades.[1] Twenty years ago, adolescent morbidity and mortality were associated predominantly with natural causes. Adolescents today, however, are endangered predominantly by their own behaviors. Drinking, tobacco and drug use, pregnancy, sexually transmitted diseases, and injuries take a major toll on youth and place them at risk of developing disease as adults. Because these health risks do not lend themselves to traditional models of medical intervention, greater emphasis is needed on prevention as a way to improve the health and well-being of adolescents.

The process of identifying and implementing a broad prevention strategy has gained momentum with the recent release of two documents by the US Public Health Service (PHS):—*Healthy People 2000: The National Health Promotion and Disease Prevention Objectives*[2] and *the Guide to Clinical Preventive Services*.[3] Unfortunately, pediatricians and other health care professionals treating adolescents have been relatively quiet in the national dialogue stimulated by these documents. Because the information contained in these two reports can, however, affect the provision of health care to adolescents, they are worth reviewing.

Healthy People 2000 was developed to focus ". . . a national strategy for significantly improving the health of the Nation over the coming decade."[2] The initiative promotes three broad health goals: "(1) increase the span of healthy life for Americans; (2) reduce health disparities among Americans; and (3) achieve access to preventive services for all Americans." To meet these goals, the PHS defined 22 areas for special emphasis. Eight relate to health promotion topics (eg, physical activity and fitness, mental health, and mental disorders), five involve health protection topics (eg, unintentional injuries and oral health), eight involve preventive services for targeted issues (eg, sexually transmitted disease and maternal and child health), and one relates to surveillance and data systems. Except for surveillance and data systems, each area includes health status,risk reduction, and service and protection objectives. Of the almost 300 national health objectives in the document, 45 target adolescents directly, and approximately 51 affect adolescents as part of the broader population. An introductory section of the document delineates the predominant health problems experienced by various age groups (including adolescents) and by special populations, such as people with low income, minorities, and the disabled.

The *Guide to Clinical Preventive Services*, the final report of the US Preventive Services Task Force,[3] describes 169 clinical screening, counseling, and immunization practices recommended for treatment or therapy of 60 target conditions. The procedures are grouped by patient age, including preadolescents (aged 8 to 12 years), young adolescents (aged 13 to 17 years), and older adolescents (aged 18 to 24 years). Only those conditions for which effective preventive intervention procedures exist or that cause a high "burden of suffering" were addressed in the report. Most of the conditions relating to adolescents qualified for inclusion in the latter category.

For at least four reasons, these two documents are important to those who work to improve the health of adolescents. First, they direct the debate on improving adolescent health to developing and implementing more effective preventive strategies. Most adolescent preventive interventions now are provided by schools, churches, youth organizations, or media campaigns. Not only do the PHS documents promote these methods of intervention, but they also renew interest in how physicians and other health care providers can provide effective preventive services in the office. Second, these documents present a framework for actions that can be taken by both the private and public health sectors. They provide impetus for the development of new strategies for physicians and health professionals who work in both traditional (eg, hospitals and private, community, and public health clinics) and nontraditional (eg, school clinics, correctional institutions, and drop-in centers) settings. Third, *Healthy People 2000* provides a structure for focusing human and financial resources. States, communities, and health organizations can use it to determine health priorities for their populations. With clearly defined objectives, organizations and health care professionals can better coordinate their efforts, producing a more efficient and comprehensive preventive health strategy. As called for in the recent report from the National Commission on the Role of the School and the Community in Promoting Adolescent Health,[4] better access to appropriate, comprehensive, coordinated, and confidential health services is necessary to solve the complex array of adolescent health problems. Providing such services will require cooperation and focused efforts from all segments of the health care community. Fourth, the PHS documents set goals that provide opportunities that allow for research on the effectiveness of various prevention strategies. As preventive interventions are developed and implemented, a rigorous agenda for evaluation of research must be followed to determine how best to use scarce health care funds.

Neither the national health objectives nor the *Guide to Clinical Preventive Services* has received universal approval. The public health care community is concerned that the national health objectives ". . . have no implementation plan, they overemphasize individual responsibility, and they abrogate governmental responsibility."[5] Critics also state that preventive health goals cannot be achieved without additional federal funding and that the multifunded nature of the US health care system precludes effective implementation.[6] The professional pediatric community has criticized the *Guide* because it recommends a specified frequency of preventive health visits for adults while leaving the frequency of such visits by adolescents and children to the discretion of the provider.[7] Other concerns are that the recommendations do not include all pediatric preventive health practices and that they tend to overemphasize change in existing behavior rather than focusing on anticipatory guidance as a way to prevent the onset of health-compromising behavior. In general, the *Guide* fails to recognize many of the risks that endanger adolescents specifically and the opportunity for promoting healthy behaviors during this developmental period. Although the *Guide* clearly "shortchanges" children and youth, it and *Healthy People 2000* together provide health professionals, administrators, and the federal government a structure on which to build sound preventive health strategies for adolescents.

It is important that advocates of adolescent health work to ensure that the interests of adolescents are well represented as the nation begins to implement broad intervention strategies for preventive health. Because adolescents and children are not empowered politically, adolescent health concerns easily may be overshadowed by concerns of other populations.

Various organizations have been funded by the PHS to promote the national health objectives as they relate to special populations or settings, such as Hispanics, blacks, schools, and hospitals. As part of these efforts, the American Medical Association received funds to be used in the dissemination of information related to adolescents. For information on this initiative for adolescents, write to the Department of Adolescent Health, AMA, 515 N State St, Chicago, IL 60610. For general information, write to the Office of Disease Prevention and Health Promotion, Department of Health and Human Services, Washington, DC 20201.

ARTHUR B. ELSTER, MD
Department of Adolescent Health
American Medical Association
515 N State St
Chicago, IL 60610

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Laboratory Test Interactions: Sensitive tests (e.g., Latex Agglutination Kits) may detect PRP derived from the vaccine in urine of some vaccinees for up to seven days following vaccination with PedvaxHIB; in clinical studies with PedvaxHIB, such children demonstrated normal immune response to the vaccine.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: PedvaxHIB has not been evaluated for its carcinogenic or mutagenic potential or for its potential to impair fertility.

Pregnancy: *Pregnancy Category C:* Animal reproduction studies have not been conducted with PedvaxHIB. It is also not known whether PedvaxHIB can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. PedvaxHIB is not recommended for use in pregnant women.

ADVERSE REACTIONS: In early clinical studies involving the administration of 8,086 doses of PedvaxHIB alone to 5,027 healthy infants and children 2 months to 71 months of age, PedvaxHIB was generally well tolerated. No serious adverse reactions were reported. During a two-day period following vaccination with PedvaxHIB in a subset of these infants and children, the most frequently reported adverse reactions, excluding those shown in the first table, in decreasing order of frequency, included: irritability, sleepiness, respiratory infection/symptoms, and ear infection/otitis media. Urticaria was reported in two children. Thrombocytopenia was seen in one child. A cause-and-effect relationship between these side effects and the vaccination has not been established.

Selected objective observations reported by parents over a 48-hour period in infants and children 2 to 71 months of age following primary vaccination with PedvaxHIB alone are summarized in the first table.

In The Protective Efficacy Study, 4,459 healthy Navajo infants 6 to 12 weeks of age received PedvaxHIB or placebo. Most of these infants received DTP/OPV concomitantly. No differences were seen in the type and frequency of serious health problems expected in this Navajo population or in serious adverse experiences reported among those who received PedvaxHIB and those who received placebo, and none was reported to be related to PedvaxHIB. Only one serious reaction (tracheitis) was reported as possibly related to PedvaxHIB and only one (diarrhea) as possibly related to placebo. Seizures occurred infrequently in both groups (9 occurred in vaccine recipients, 8 of whom also received DTP; 8 occurred in placebo recipients, 7 of whom also received DTP) and were not reported to be related to PedvaxHIB. The frequencies of fever and local reactions occurring in a subset of these infants during a 48-hour period following each dose were similar to those seen in early clinical studies (see first table).

As with any vaccine, there is the possibility that broad use of PedvaxHIB could reveal adverse reactions not observed in clinical trials.

Potential Adverse Reactions: The use of Haemophilus b polysaccharide vaccines and another Haemophilus b conjugate vaccine has been associated with the following additional adverse effects: early onset of Haemophilus b disease and Guillain-Barré syndrome. A cause-and-effect relationship between these side effects and the vaccination was not established.

Fever or Local Reactions in Subjects 2 to 71 Months of Age Vaccinated with PedvaxHIB Alone: Other Clinical Studies

		Dose 1				Dose 2			
Age (Months)	Reaction	Number of Subjects Evaluated	6 hr.	24	48	Number of Subjects Evaluated	6 hr.	24	48
2-14*	Fever >38.3°C (101°F) Rectal	532	2.4%	3.8%	1.9%	329	3.0%	4.3%	3.6%
	Erythema >2.5 cm diameter	1,026	0.2%	1.0%	0.4%	585	0.9%	1.2%	0.7%
	Swelling/ Induration >2.5 cm diameter	1,026	0.6%	1.5%	1.6%	585	0.9%	2.8%	3.7%
15-71**	Fever >38.3°C (101°F) Rectal	149	4.0%	4.0%	6.7%				
	Erythema >2.5 cm diameter	572	0.0%	0.3%	0.2%				
	Swelling/ Induration >2.5 cm diameter	572	0.9%	2.1%	1.4%				

*Additional complaints reported following vaccination with the first and second dose of PedvaxHIB, respectively, in the indicated number of subjects were: nausea, vomiting, and/or diarrhea (101, 41), crying for more than one-half hour (43, 15), rash (16, 17), and unusual high-pitched crying (4, 4).

**Additional complaints reported following vaccination with one dose of PedvaxHIB in the indicated number of subjects were: nausea, vomiting, and/or diarrhea (44), crying for more than one-half hour (19), rash (12), and unusual high-pitched crying (0).

DOSAGE AND ADMINISTRATION:

FOR INTRAMUSCULAR ADMINISTRATION. DO NOT INJECT INTRAVENOUSLY.

2 to 14 Months of Age: Infants 2 to 14 months of age should receive a 0.5-mL dose of vaccine ideally beginning at 2 months of age followed by a 0.5-mL dose 2 months later (or as soon as possible thereafter). When the primary two-dose regimen is completed before 12 months of age, a booster dose is required (see text and second table).

15 Months of Age and Older: Children 15 months of age and older previously unvaccinated against Haemophilus b disease should receive a single 0.5-mL dose of vaccine.

Booster Dose: In infants completing the primary two-dose regimen before 12 months of age, a booster dose (0.5 mL) should be administered at 12 months of age but not earlier than 2 months after the second dose.

DATA ARE NOT AVAILABLE REGARDING THE INTERCHANGEABILITY OF OTHER HAEMOPHILUS b CONJUGATE VACCINES AND PedvaxHIB® (Haemophilus b Conjugate Vaccine [Meningococcal Protein Conjugate], MSD).

Vaccination Regimens by Age Group
(see text for details)

Age (Months) at First Dose	Primary	Age (Months) at Booster Dose
2-10	2 doses, 2 months apart	12
11-14	2 doses, 2 months apart	—
15-71	1 dose	—

TO RECONSTITUTE, USE ONLY THE ALUMINUM HYDROXIDE DILUENT SUPPLIED. First, agitate the diluent vial; then, using sterile technique, withdraw the entire volume of aluminum hydroxide diluent into the syringe to be used for reconstitution. Inject all the aluminum hydroxide diluent in the syringe into the vial of lyophilized vaccine, and agitate to mix thoroughly.

Withdraw the entire contents into the syringe and inject the total volume of reconstituted vaccine (0.5 mL) intramuscularly, preferably into the anterolateral thigh or the outer aspect of the upper arm.

It is recommended that the vaccine be used as soon as possible after reconstitution. Store reconstituted vaccine in the vaccine vial at 2° to 8°C (36° to 46°F) and discard if not used within 24 hours. Agitate prior to injection.

Parenteral drug products should be inspected visually for extraneous particulate matter and discoloration prior to administration whenever solution and container permit. Aluminum hydroxide diluent and PedvaxHIB when reconstituted are slightly opaque white suspensions.

Special care should be taken to ensure that the injection does not enter a blood vessel.

It is important to use a separate sterile syringe and needle for each patient to prevent transmission of hepatitis B or other infectious agents from one person to another.

HOW SUPPLIED: No. 4792–PedvaxHIB is supplied as a single-dose vial of lyophilized vaccine, NDC 0006-4792-00, and a vial of aluminum hydroxide diluent.

No. 4797–PedvaxHIB is supplied as follows: a box of 5 single-dose vials of lyophilized vaccine, NDC 0006-4797-00, and 5 vials of aluminum hydroxide diluent.

Storage: Before reconstitution, store PedvaxHIB at 2° to 8°C (36° to 46°F). Store reconstituted vaccine in the vaccine vial at 2° to 8°C (36° to 46°F) and discard if not used within 24 hours.

DO NOT FREEZE the aluminum hydroxide diluent or the reconstituted vaccine.

For more detailed information, consult your MSD Representative or see Prescribing Information.
Merck Sharp & Dohme, Division of Merck & Co., INC., West Point, PA 19486.

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JOVA08(802)

Redoing the Health Care Quilt

Patches or Whole Cloth?

William W. Cleveland, MD

The current health care system of the United States, like a quilt that is tattered and full of holes, badly needs attention. The question is whether we should repair it with patches or replace it with a new quilt of whole cloth. That the system needs fixing is evident; the deficiencies have been described by abundant commentaries. The major deficiencies include those cited below.

The Uninsured.—An estimated 37 million people in the United States do not have health insurance. Of these, about 12 million are children; another major segment comprises pregnant women. These numbers are estimated to have increased approximately 30% in the last decade. This reflects lack of employee coverage, particularly in small businesses, and a high rate of job turnover. It also reflects an inadequate Medicaid program that varies by state but that generally leaves a significant fraction of indigent families uncovered. The problem of uninsured children has been extensively reviewed by Oberg.[1]

Expanding Health Care Costs and an Apparent Lack of Efficiency.—If infant mortality rate is an acceptable indicator of maternal and child health, the comparison of rates in the United States with those of other nations relative to expenditure provides a discouraging picture indeed (Fig 1).[2] Our per capita medical expenditure is the highest in the world, but we rank 21st in infant mortality rates. When infant mortality rates are compared in terms of percentage of gross national product spent on health care, the result is the same (Fig 2). One factor to be considered is whether the US government is spending its money in the right places. For example, if infant mortality rates among developed nations are compared with the percentage of health care dollars spent for public health, our position is reversed—the United States spends the lowest percentage for public health and is still 21st in mortality rate (Fig 3).

A Burdensome Bureaucracy.—Costs of administering US health care programs are staggering. Of the approximately 11.5% of the gross national product expended, an estimated 2.6% funds the bureaucracy. For the physician, penetrating the administrative barriers of either governmental agencies or insurance companies to render service charges is a familiar problem. For the patient, dealing with these groups is perhaps even more difficult. The bureaucracy of health care appears to be in a state of chronic and self-sustained hyperplasia.

An Inadequate Medicaid Program.—This system is federally mandated but managed through varying policies by the states. These variances include the standards for inclusion in the program, the scope of benefits provided, the amount of public funds allocated, and rates of provider reimbursement. Financial criteria for eligibility vary widely, but in most states a significant portion of the indigent population of children and pregnant women is not covered. For persons eligible, the mechanisms for registration are often cumbersome and patients with limited social resources may not be able to gain access to the system. A further deficiency is that payment to providers may be so low as to offer no incentive to render services. In some states, payments for preventive care, including well-child visits, are so low that they do not cover physicians' overhead, much less reimburse them for professional services.

A Troubled Health Insurance Industry.—More than 1500 health plans in this country compete for coverage in an entrepreneurial system. Each maintains its separate administration; each has its own policies as to eligibility and coverage and each is a for-profit operation. Providers must deal with a variety of provisions and regulations that significantly contribute to costs of delivering care. Insurance companies also must spend large amounts of money on administrative costs—approximately 12% of premiums.

Lack of Emphasis on Prevention.—The insurance industry does not embrace preventive medicine as its goal. Pediatricians in Florida were able to promote legislation mandating well-child care provision by insurers; this was accomplished with great travail and with much resistance by the industry. As previously noted, an inordinately low percentage of our health care funds goes to public health agencies. Medicaid struggles to provide treatment of illness with incomplete success, and little is left for preventive care.

Litigious Factors Expanding Costs.—Physicians who practice in areas where malpractice suits flourish and attorneys become rich cannot help but be influenced by this threat in making clinical decisions. The remote chance that a child not growing well has a hypothalmic lesion not clinically evident provokes the performance of magnetic resonance imaging, which currently costs $1200. (Why this procedure should cost $1200 or growth hormone should cost $50/mg is also of interest, but that is the subject of

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From the Department of Pediatrics, School of Medicine, University of Miami (Fla).

Reprint requests to Department of Pediatrics, PO Box 016980 (R 131), Miami, FL 33101 (Dr Cleveland).

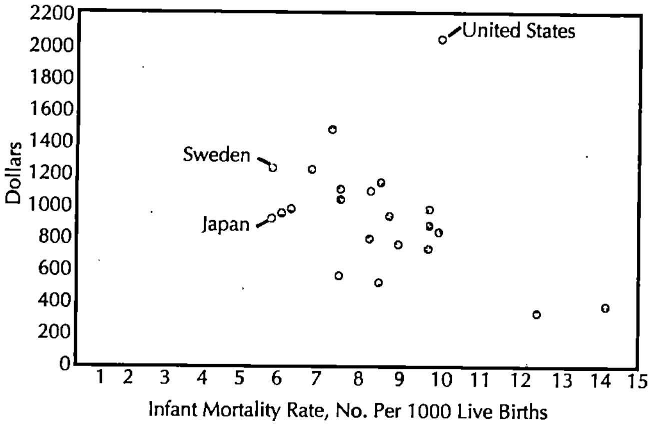

Fig 1.—*Per capita health expenditures and infant mortality rates in 1987.*

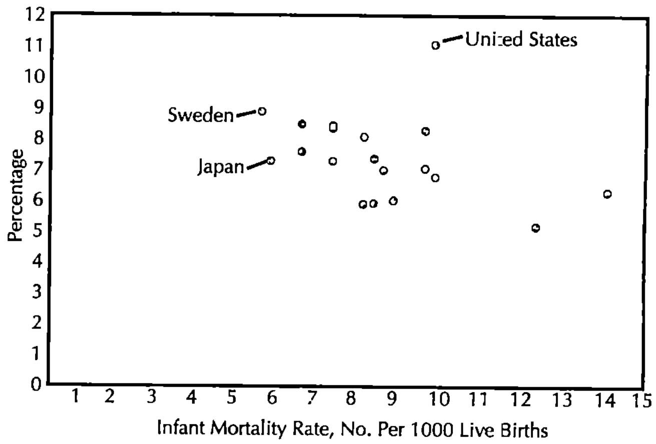

Fig 2.—*Infant mortality rates and public health expenditures as percentages of all health expenditures in 1987.*

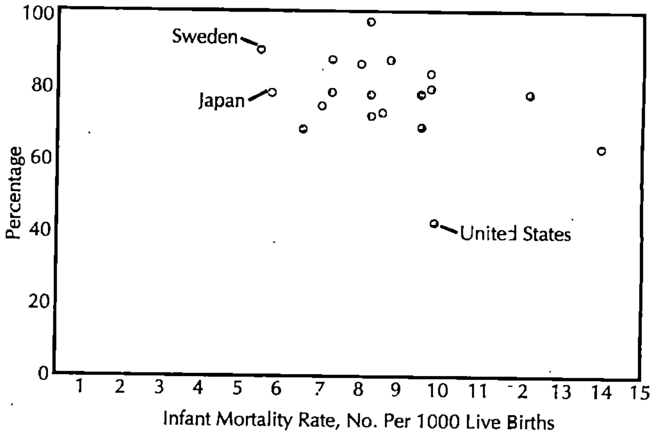

Fig 3.—*Infant mortality rates and health expenditures as percentages of gross national product in 1987.*

another essay.) And so it goes—the expansion of these ultraconservative decisions contributes to health care costs, to say nothing of its contribution to the costs of malpractice insurance. The many holes in the ragged quilt are evident. All agree that repairs are urgently needed. The question remains as to the best approach. Many alternatives have been proposed—patches and new quilts of whole cloth.

THE PATCHES

Various proposals have been made at several levels to patch the holes. The essential features of some of these are summarized below. The review is intended to be illustrative but not all-inclusive.

Medicaid Expansion and Reform.—This is a part of several proposals listed below, but has been specifically addressed by the Health Policy Agenda for the American People.[3,4] Eight major reforms were recommended by the Ad Hoc Committee on Medicaid and are as follows:

1. The Medicaid program should be governed by national standards and goals.
2. The categorical link of Medicaid eligibility to public cash assistance (welfare) programs should be broken; income eligibility for the program should be set at no less than the federal poverty level.
3. All states should be mandated to adopt a Medically Needy program with "spend down" eligibility provisions. Asset testing should be an acceptable eligibility requirement only through the Medically Needy provisions. "Medically needy" persons are those whose incomes exceed the Medicaid eligibility level but who have been impoverished by catastrophic medical bills.
4. A standard benefit package should be provided by each state and federally mandated. It should include physician services, inpatient and outpatient hospital services, laboratory and roentgenogram services, prescription drugs, institutional care for the elderly and the physically or mentally disabled, dental services, early and periodic health screenings, diagnostic and treatment services, family planning services, home health and personal care services, and other medically necessary professional services.
5. Medicaid expansion should include measures to promote cost-effective provision of services.
6. Medicaid expansion should include policies and incentives to encourage broader health care provider participation.
7. A greater burden of the fiscal impact of eligibility expansion should be borne by the federal government, and the federal formula governing reimbursement to states should be revised to correct for tax-burden inequities.
8. Long-term care services should be continued under Medicaid or through a structurally improved program.

Basic Health for All Americans Act.—Proposed by Kennedy[5] in 1987, the act recommends major expansion of employer coverage for health care and mandates a minimum level of health benefits to be provided, including hospital and physician care, preventive testing, prenatal testing, and well-baby care.

Universal Maternal and Child Health Program.—Proposed by Oberg,[1] this would ensure universal and equitable access to health services by pregnant women and children independent of age, income, family composition, or employment. Coverage would be provided for preventive as well as acute and catastrophic services.

Recommendations of the Pepper Commission.—The commission's recommendations[6,7] include insurance reforms by which income-based cost sharing of premiums by employers and a public plan guaranteeing health care coverage for all workers would be implemented. Ultimately, this plan would provide coverage for all children. Insurance reforms would include coverage of primary and preventive care, elimination of exclusions because of preexisting conditions, and elimination of coinsurance payments by consumers for prenatal and well-child care. The commission also recommended Medicaid reforms (including physician reimbursement for obstetric and pediatric care), ultimate replacement of Medicaid with a new federal program expanding access and payment according to Medicare rules, a quality assurance strategy that would lude reform of the medical malpractice system, and cost tainment measures.

merican Academy of Pediatrics National Child alth Policy.—This policy[8] includes health care coverage all children and adolescents through age 21 years and ndates employer-based coverage or coverage by pri- e insurance companies contracted by the state. The pol- also calls for state health care funding (including fund- of Medicaid expenditures), state and federal insurance emiums, an employer payroll tax for those employers o choose not to cover pregnant women and children, d methods of ensuring adequate provider reimburse- nt.

HR 4280 Health Insurance for Children and Mothers t of 1990.—This act[9] requires health insurance for preg- nt women and children, mandates comprehensive ben- ts, calls for elimination of financial barriers to health care evelopment of a one-tier health care system), recom- nds that Medicaid dollars be refocused in a more ef- ient and effective program, emphasizes preventive ser- es (including immunizations, and prenatal and well- ild care), and directs that payroll tax be increased to atch current Medicare tax paid by employer and em- oyees.

A Consumer Choice Health Plan for Universal Health surance.—The proposal[10] states that "To remedy the privation, we propose that everyone not covered by edicare, Medicaid, or some other public program be en- led to buy affordable coverage, either through their em- oyers or through a 'public sponsor.' To attack the excess, e propose a strategy of managed competition in which llective agents, called sponsors, such as the Health Care nancing Administration and large employers, contract ith competing health plans and manage a process of in- rmed cost-conscious consumer choice that requires pro- ders who deliver high-quality care economically."

State Programs.—These programs include Massachu- tts legislation designed "to make health security avail- le to all citizens of the Commonwealth and to improve ospital financing." This legislation would create a De- artment of Medical Security that contracts with health ans to make coverage available to small businesses and nsponsored individuals. It proposes a tax on all employ- 's of five or more workers.[11] The New York State De- artment of Health has developed a program called Uni- ersal New York Health Care, or UNY-CARE.[12] It would tain existing payers, including employer-based insur- nce coverage, but would combine them in a one-payer amework. This one payer would be the only resource for ost services and would negotiate reimbursement rates, opefully to exercise some cost controls.

Rationing Health Services.—Oregon legislation pro- oses altering Medicaid coverage to provide services ased on a "net benefit" concept.[13] This involves priori- zing medical services on the basis of cost and benefit to e overall public. A list of such priorities has been gen- rated. Different priorities have been established for dif- erent age groups. High priorities are given to family plan- ing, prenatal care (including nutritional care), childhood nmunizations, labor and delivery services, and the treat- ent of acute illness. Low-priority items include infertility ervices, plastic surgery, routine dental care for adults, nd most transplantations. These priorities are established y a Health Services Commission consisting of five phy- icians, a public health nurse, a social worker, and four onsumers. The basic principle is expansion of numbers erved by restriction of services provided. Thus far it pro- oses rationing services only to those served by Medicaid.

Rationing Medical Progress.—Callahan[14] describes his proposal as follows: "In any case, we must be prepared to ration medical progress and in particular to forego potentially beneficial advances in the application and development of new techniques. I am not proposing a diminution of efforts to extend our store of theoretical biologic and medical knowledge. A strong commitment to basic biomedical research remains an attractive and desirable goal. That commitment is not incompatible, however, with several insistent requirements: (1) that clinical applications be subjected to stringent technological assessments before dissemination; (2) that the social and economic standards for the assessment be biased toward restrictiveness ('straight is the gate and narrow the way' might be a pertinent maxim here); and (3) that it is understood and accepted that some, perhaps many, beneficial applications will have to be passed over on grounds of cost and other, more pressing social priorities."

Rationing Health Care According to Age.—Levensky[15] summarized these proposals as follows: "Why is it acceptable to propose limits on health care for the elderly, in contrast to the obvious unacceptibility of such a proposal applied to other groups and classes of citizens? A number of philosophers and medical ethicists, prominent among them Callahan, Daniels, and Veatch, have published carefully formulated arguments favoring the use of age as a criterion for rationing health care. Although the details of their various arguments differ, the essential philosophical underpinnings are quite similar. They argue that limits on health care for the elderly are justifiable because each citizen, throughout a lifetime, would benefit if funds now used to extend life at its end were redirected to earlier stages of life. They envision the national health care budget equitably distributed among all citizens. Each person would be entitled to a fair share of national health care expenditures as a personal lifetime 'health care budget.' "

THE QUILTS

The Canadian Health Care System

Much discussion of adopting a variant of the Canadian system has been heard.[16] In Canada, one national health program is administered by the provinces, and universal coverage for all citizens is provided regardless of age, health status, or financial means.

All medical costs, with no copayments or deductibles and including costs of long-term stays in health care facilities, are covered. Services include care by physicians in offices, in hospitals, and at home. Also covered are diagnosis and treatment of illness and injury (including and drugs prenatal and postnatal obstetrical care); laboratory, radiologic, and other ancillary services; radiotherapy; and home dialysis. Most of the provinces also provide land and air ambulance services. Private or semiprivate hospital accommodations are not covered by the plan but may be financed through commercial insurers with premiums paid by employers. (These plans may not, however, offer benefits provided by the provincial plans.)

Payments to providers include fee-for-service reimbursement of physicians according to a schedule negotiated between organized medicine and provincial government. Some provinces have capitation systems. Patients can choose any physician. Extra billing by physicians is barred. Hospitals are paid an annual global sum for provision of services, which is similarly negotiated. In Canada, centralized government controls are exercised over major forms of technology and capital spending, with an effort to regionalize highly technologic services. The system is financed by payment of premiums by employers and individuals. Funding is also provided by the provincial and federal governments through general revenues. Participants older than age 65 years pay no premiums; individuals or families lacking resources to pay also are not charged.

Comprehensive Health Care for All Americans Act (the Claude Pepper Comprehensive Health Care Act)

This comprehensive plan includes many features of the Canadian system.[17] Its principal elements are as follows:

Eligibility.—All residents of the United States who are citizens, nationals, or lawful resident aliens may enroll. The enrollee may choose among qualified health plans as approved by the state of residency.

Administration.—The act would establish a National Comprehensive Health Care (CHC) Board to which each state would submit a plan for its CHC program. To be approved, the state plan must provide for (among other things): adequate financing, freedom of choice among qualified health plans by enrollees, effective cost containment measures, adequate administration (including establishment of a public advisory boards), responsive quality control mechanisms, and organization of a state commission to reduce excess hospital beds. The National CHC Board would establish a commission to provide advice regarding technology development and effectiveness and to recommend such technologies for inclusion as covered health services. Each state CHC program would approve qualified health plans for inclusion based on defined criteria. The number might be limited, except for health maintenance organizations.

Financing.—The federal CHC program would make a per capita contribution to each state annually according to defined criteria for support of the state plan. The state CHC program would generate funds from general revenues, earmarked taxes, sales taxes, employer and employee health insurance premiums, and cost sharing. Services for low-income groups, pregnant women, and well-child care might be exempt from premiums or cost sharing.

Reimbursement.—The CHC program would include payment of institutions according to a biennial budget plan and to physicians according to payment schedules negotiated with medical organizations and based on a national relative value scale. Alternate methods such as capitation, annual salary, and hourly payments might be approved with some restrictions.

Benefits.—The plan provides very broad coverage, including physicians' and other professional medical services, inpatient and outpatient hospital care, diagnostic and screening tests, prenatal and well-baby care, mental health services, long-term care, and hospice services. Preventive services would include basic immunizations, prenatal and postnatal care, well-child care (including periodic physical examinations and hearing and vision screening until age 23 years), Papanicolaou smears, and mammographic examinations. This legislation also proposes extensive programs for long-term and geriatric care and authorization for support of research of acquired immunodeficiency syndrome, hypertension, sickle cell anemia, infant mortality, and breast cancer.

Mediplan

This proposal mandates a broad health care program[18] by which all US residents would be enrolled and issued a Mediplan card entitling them to care. Subsequently, residents would be enrolled at birth. Children, pregnant women, and low-income groups particularly are identified to receive services. Benefits would include those provided currently by Medicare and special preventive health services for women and children (including well-child care and pregnancy-related services). Providers would be paid according to a resource-based relative value scale. Physicians would be required to accept a Mediplan rate and charge no additional fees. Mediplan includes a global obstetrical fee and a bonus for prenatal care. Children, pregnant women, and low-income groups would be exempt from the $500 annual deductible. Financing of Mediplan would be generated from income tax, employer contributions, and income-related employer premiums. Deductibles, copayments, and co-insurance would be limited to $2500 per year.

A National Health Program for the United States: A Physician's Proposal

Himmelstein et al[19] and Woolhandler and Himmelstein,[20] along with the Writing Committee of the Working Group on Program Design representing Physicians for a National Health Program, describe a comprehensive health plan by which everyone would be covered by one public plan and all alternative insurance coverage, copayments, and deductibles would be eliminated. All medical services, including those to treat acute problems and problems requiring long-term and rehabilitative care, would be covered. Prevention and public health programs would be covered, as would dental services and occupational therapy. A lump-sum budget would be negotiated annually with hospitals for patient services. Improvements, expansion, and major capital services would be funded by independent appropriations. Three options would be available: fee-for-service, salaried positions in institutions receiving global budgets, and per capita payments to group practices or health maintenance organizations. Fee schedules would be negotiated by a medical organization, and extra billing would be limited to uncovered services such as cosmetic surgery. All funding sources currently used would continue during a transitional period (including insurance premiums, Medicaid, Medicare, and employer contributions), but all would flow through a single payer, the national health plan. Private health insurance would be phased out over 3 years, and general tax revenues would be developed based on income or some other progressive tax.

COMMENT

Most would agree that our health care system needs urgent attention. There are obviously many options. The continuing flow of thoughtful commentaries on the problem in our medical journals[21-34] reflects the intense interest of health care professionals. Various polls have demonstrated that Americans favor a major overhaul of the health care system, but their dissatisfaction has apparently not reached a level sufficient to bring pressure on politicians, which is ultimately needed if change is to occur. In contrast, powerful elements in the health care industry exert major influence in determining changes or lack thereof. As Levey and Hill[21] put it: "The voices now raised to support national health care will not produce universal health insurance soon . . . . Americans lack a necessary level of discontent with our health care system, agreement on a widely endorsed program of universal health insurance, and the political stamina to drive legislation through Congress." However, perhaps enlightened leadership in the medical community can stimulate the necessary action in both lay and professional circles. Relman,[22] in a valuable discussion of the subject, reviews the options and concludes: "In my view, nothing short of a comprehensive plan which includes improved technology assessments and malpractice reform as well as other reforms of medical practice is likely to achieve the goals of universal access, cost containment and preservation of quality that everyone seems to want. . . . Now is the time for our profession to make common cause with government and with the major private payers in seeking solutions to a pressing social problem that is not going to solve itself."

If political and other realities limit us to patches, even if in the process of shopping for a new quilt, then we should get on with it. The most practical of these is modification of the Medicaid program: extended coverage for indigent children and pregnant women; increased benefits provided, with emphasis on preventive care; and payments to providers that are adequate to attract their services. These changes can be relatively simply made by federal and state governments. This is an urgently needed first step that can be taken while plans for broader coverage are being developed. Medicaid expansion in one or another form is part of several broader recommendations, including the legislation proposed by Stark,[8] the American Academy of Pediatrics,[9] and, at least temporarily, the Pepper Commission.[5,6] If we pursue patchwork remedies, these broader proposals should be evaluated as to overall benefit and political reality.

A modification of the Medicaid patch proposed by the state of Oregon would ration services based on net benefit. (This is in contrast to our present system of rationing care by limiting populations served.) This proposal has generated much and varied reaction.[13,23,24] Variations on this idea causing even more violent reactions have included Callahan's proposal[14] to ration new technology and a scheme to ration services based on age, restricting access to some benefits by the elderly. The Canadian system controls provision of some services by having the health plan approve implementation of new technology in clinical practice and by controlling capital expenditures by institutions. The chances of implementing any of these proposals seem slim.[24]

If we are to consider a new quilt, how should it be sewn? The Canadian system has been much discussed[25-28] and has many advantages: universal coverage under one plan; coverage of all reasonable benefits; one system of management that simplifies procedures for patients, physicians, and hospitals; free choice of physicians; emphasis on the role of the primary care practitioner; regulated application of new technology that encourages regionalization; controlled capital expenditures; fee-for-service physician reimbursement; and controlled hospital costs through development of an annual, realistically-negotiated budget. Studies comparing the Canadian and American health care systems[27,28] have emphasized reduced administrative costs in Canada, costs that contribute to premiums for patients and to overhead for physicians in the United States. The cost of health care in the United States is approximately 11% of the gross national product, while in Canada it is approximately 8%, despite the latter's broader coverage. The difference has been attributed largely to our higher administrative costs, higher payments to physicians, and hospital costs. Concerns about the Canadian system include its larger role of government and the potential of increased regulation, yet there is apparently more regulation of clinical practice in this country than in Canada. Evans et al[28] point out that "In the United States corporate competitors or employers may turn out to be more ruthless than public regulators." Another concern, not so regularly expressed, is the impact on physician's incomes. A comparison of fee costs in 1985[27] revealed the following ratios for some services.

Service	Fee Ratio, United States to Canada
Surgery	3.21:1
Anesthesiology	3.73:1
Radiology	3.50:1
Office visit	1.56:1
Hospital visit	4.77:1

A comparison of net physician incomes (US physicians vs Canadian physicians) produced a ratio of 1.35:1, and, according to one report, after adjustment for costs of resources (including liability insurance) the ratio became 1.30:1.[16] In 1984, the mean net income of physicians (before taxes) in Ontario was $160 000 per year for specialists and approximately $112 000 for general practitioners. Another report[27] lists net income for office-based physicians in Canada in 1985 as $73 607, compared with $112 109 in the United States. Interestingly, this report states that payments to physicians (before income taxes) represent 52% of the gross income in the United States and 66% in Canada.

The United States needs a health care system that will provide access to coverage by all citizens. It must provide services of broad scope and high quality, and it must do so with emphasis on measures for cost containment and preventive health. The evidence seems compelling that this can be done only by the institution of a new system. As Iglehart[25] puts it, "Muddling through, as we are now doing, is not a prescription for the ages, nor is it a policy that allows the United States to stand tall." Of the options, a variant of the Canadian system appears most attractive. The program described by Himmelstein et al[19,20] embraces many of the desirable features and would be a new, first-class quilt, but quilts imply bedfellows, and it is desirable, almost essential, that bedfellows be compatible. There are a number of large fellows in the bed, including the health insurance industry, hospitals, employers, government, politicians, and the public. The chances of compatibility under a new quilt seem remote, particularly when some bedfellows may get kicked out of bed. Nevertheless, it is imperative that we keep trying and that the medical profession lead the efforts to ultimately find a new quilt rather than to continue patching the old one.

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A Regional Pediatric Approach to the Epidemic of Social Ills Within Our Cities

Waldo E. Nelson, MD

'Twas midsummer 1990, I received a letter from Vince Fulginiti:

> In May 1991, each of the AMA family of journals will devote all or most of their issues to articles that report individual and professional societies' ideas and suggestions for improving health care to the poor and underserved in this country. *AJDC* will focus on infants, children, adolescents, and young adults. . . who are not receiving it [health care] currently, or who are poorly served by our present system. . . . This would be an excellent opportunity . . . for you to [record] your concept of the academic health center/community relationships . . . [for the health care of] the underserved and unserved . . . ."

Vince (my one-time student, now colleague, and from the beginning, my teacher) is correct in his implication that an overriding concern of mine is that the state of our national health care is not nearly as good as it could be. The most serious deficits are evident in the health care available for the poor and are, to a great extent, concentrated in our large metropolitan areas. The issue at hand for the medical community appears to be not only the search for ways to improve the quality of health care, but also for an adequate distribution of it and the means to pay for it. This is not a new concept. My own recognition of these inadequacies goes back to the mid 1920s.

No attempt will be made here to review the many aspects of this multifaceted subject. Rather, I venture to suggest an initiative for medical care of the underprivileged that may have some potential to be effective now, and even to provide some serendipitous dividends for the future.

I am convinced that more is likely to be gained at the local level within an area or region that functions as a natural medical service unit rather than by a limited national program. In recent years there have been several national programs designed to provide care for the socioeconomically deprived, especially within the inner cities. At best they were of limited value and were relatively expensive.

The medical unit in this concept is a regional area with complete primary, secondary, and tertiary medical services for its inhabitants. In general, they are not demarcated by state or other political boundaries, but have been determined by growth and developmental factors within and around urban centers and extend into the surrounding rural areas. Primary services are those available through physicians in private practice, in particular, pediatricians, internists, family practitioners, and pediatric nurse practitioners, and through their respective counterparts in the community and tertiary hospitals.[1]

The regional medical unit will contain a number of neighborhood hospitals (secondary), and at least one tertiary (usually associated with a medical school) hospital. In most large metropolitan areas there are usually two or more medical schools. Each hospital will naturally have its own coterie of practicing physicians who preferentially refer their patients who need specialized care. Hospitals that have attained particular competence in a certain highly specialized clinical field should expect preferential referrals to them from the primary physician whose principal affiliation is with another tertiary hospital and even from the clinical staffs of other academic hospitals. If such an objective policy were adhered to, it would represent a major step toward high-quality care in that regional medical unit.

For such a utopia to come into existence, not only goodwill but free and open communication among the physicians within that region will be required. Furthermore, it will necessitate elimination of competitive advertising by hospitals, health maintenance organizations, and individual physicians. To be sure, such activity is not only condoned by the federal government, it is even encouraged, and so far as I am aware, it is not objected to by AMA-related societies. It can only be destructive in some of its current forms. Information about services available in the various hospitals, health maintenance organizations, and other medical service units is essential for the primary physician and for the lay public, but inflammatory advertising that is unjustly self-serving should be abolished.

What I speak for is simply a realistic bonding between practicing physicians and those in academia in accepting responsibility for the quality of medical care within and "beyond their office walls," ie, within their respective region. I tend to designate those physicians who are primarily in private practice as "The Town" and those who are solely or mainly in academic activities as "The Gown."[2] It is the close integration of these physicians within a given region that is so essential in determining the ways and means to meet the medical needs of the underserved.

Those of us in the medical field should sense our personal responsibility not only for the quality of medical care in our respective roles, but also for the quality of health care within our community.[1] For example, activities centered more or less in the Philadelphia Pediatric Society,

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From the Department of Pediatrics, Temple University School of Medicine at St Christopher's Hospital for Children, Philadelphia, Pa.

Reprint requests to CME office, St Christopher's Hospital for Children, Erie Ave at Front St, Philadelphia, PA 19134-1095 (Dr Nelson).

concerning the epidemic proportions of socioeconomic health problems among children and youth in our area, led to the formation of a task force under the leadership of William N. Mebane, MD, Director of the Family Practice Residency Program at the Chestnut Hill (Pa) Hospital. It was thought that this group could bring together those in the Gown sector (medical school hospitals) who were currently involved in pediatric activities in public schools and in shelters for the homeless with members of the Town sector who might be interested in sharing in this work. Both resident physicians and medical students are becoming involved in these activities.

Recently, the Philadelphia Pediatric Society circulated a questionnaire among its membership to identify additional Town and Gown physicians who might be interested in joining in this work. To date, there have been some 120 favorable replies. It will be of considerable interest to see what eventually evolves from these activities.

One of the recent encouraging outcomes has been the "spontaneous creation" by the resident physicians from one of the hospitals of a volunteer group of their own to provide medical services at an evening clinic in one of the shelters, an activity that does not interfere with their hospital program. I visited an evening clinic recently. It was a busy sight that included mothers, some fathers, infants and children, doctors, a nurse, and two social workers. It was truly a rewarding experience. Had one not known, one would not have surmised the variety of medical problems that were represented.

A necessary step will be the funding of this local effort. At the moment it is expected that the salaried members of the pediatric departments will continue receiving their current support, and it is hoped that, at least for the foreseeable future, the private physicians from the Town will "gain most," if they serve on a volunteer basis. In days past, when the Town was so essential in sharing in the clinical teaching load of pediatric departments, most of them served without pay. To this day, I have not found more loyal members of the two departments I was privileged to serve in my active days than those whose participation was on a volunteer basis. However, there will be a need for additional money. More can be expected from a number of sources—local governments, foundations, corporations, labor unions, and private individuals.

Separate from our considerations in support of a regional approach to the solution of community health problems is the necessity to devise a new national health insurance program that will include all persons on as nearly an equitable basis as possible. The time is past when we should expect anything less. It is estimated that 30 to 40 million of our children who are mainly in the lowest socioeconomic grouping are either uninsured or underinsured. To include them in a revised program will likely necessitate reduction in the payments to some of those in the older age group. There will be opposition, and the lobby for this group is not impotent. I am in this age group, and I am comfortable in saying that there are a number of us who could do with less in "third party payments" for care in our terminal years even if it is not the most pleasant of possibilities. The uninsured children must also be served. They have years of growth and development and of contribution to mankind ahead of them.

A national commission made up of competent, objective, and socially minded citizens should be formulated to develop such a program, and soon!

So, my concept of a common goal for those who are committed to the search for excellence in the provision of health care is simply that in each successive period, the medical care for each person, in health and in disease, will come to approximate the potentials of the moment; that such high-quality health care will be available to all those who want and can profit from it; that the lay person will recognize that he or she must come to appreciate "good care" and be responsible for cooperating with it and for maintaining a healthy pattern of living; and that the legal profession will share in attempts to develop a truly objective and ethical climate in the region.

Within our own time, what can be done by the medical profession and, especially, by the pediatric segment of it, to develop a workable plan to meet the above-mentioned goals?

1. Town and Gown will join together in determination to see "that their (invisible) walls shall come tumbling down," a true bonding.[2] Their constant priority will be to assume joint responsibility for the general health of the community in conjunction with their public health departments, including those of the school systems.
2. Town will have access to and make use of Gown's personnel and facilities, when indicated, in the treatment of their acutely ill patients as well as in the study and treatment of chronically ill ones, often on a continuing basis.
3. Gown will tap the Town segment for bolstering its teaching programs in inpatient and outpatient divisions. Some of our best teachers are among the Town personnel and some of our best clinicians among the Gown segment.[1]
4. Town and Gown will participate in efforts to devise a health insurance program available to all citizens, and everyone, including professionals and laity, will cooperate in efforts to make its operation fiscally sound.

Important as the medical aspects are, the social, educational, and economic deficits present as great or greater challenges in planning a total community program. These deficits are manifested by the lack of personal motivation among school-age children, the number of school dropouts, the failure to take advantage of work opportunities, teenage pregnancies, and other deviations that often result in anger against society, not only leading to lives of crime but to loss of potentially productive careers.

The issue at hand is patently a moral one that will not go away except by appropriate mass determination and action. It is my contention that the desired goal of giving each child the opportunities that could lead to readiness for responsible adulthood is most likely to be attained by local efforts within multiple communities.

Those of us in the health field constitute one channel of support. Within the confines of our communities, we can, in conjunction with other disciplines, the family, education, business, law and, not the least, the church, find ways to reactivate the spirit and determination to make this country truly a land of equality in freedom and in opportunity for the child to find a fulfilling role in society.

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Poverty and the Health of American Children

Implications for Academic Pediatrics

Richard B. Johnston, Jr, MD

The headline of a recent editorial in the *Philadelphia Inquirer* posed a loaded question: "How is it that we have such great hospitals—and such poor public health?" (August 22, 1989:14-A).

The reference point was Philadelphia in which "high-tech progress and abysmal public health performance . . . coexist too comfortably." Instead of just "cranking out specialists," the editorial said, "academic medicine ought to be taking stock of its broader mission—preventing sickness, making care more easily available and figuring ways to improve the state of public health." The present focus of medical schools has led to sophisticated methods of treatment but

> has left too much undone, too many unserved, in a nation with the resources and imagination to make life healthier, even for the poorest, most vulnerable of its people. . . . On matters of public health, academic medicine has been embarrassingly slow to show leadership. . . . Doctors have won heroic fights to save babies. But when it has come to shaping strategies to save generations, their record is skimpier. Medicine has been reactive, repairing the damage *after* it has been done.

The editorial was indeed provocative. The responses from the academic medicine and public health communities correctly emphasized the unfair implication that medical schools and their hospitals can be blamed for the serious health issues that affect the city. Little was said, however, in response to the editorial's basic question: What are medical school people doing to correct these health problems that affect so many humans so profoundly? The fact that the editorial's fundamental question also should have been addressed to our political leaders at a local and national level is frustrating. That so many of the city's (and the country's) people do not receive even basic medical care cannot reasonably be blamed on academic medical centers. In fact, these centers bear much of the burden of this society's failure in public health, because they spend a great deal of largely nonreimbursed time, emotion, and expertise dealing with its consequences. This underreimbursed effort, as important as it may be, makes it harder for academic medicine to accomplish its special mission of education and research.

Nevertheless, the validity of the challenge remains, and it is hard to escape the conclusion that we have a responsibility in academic pediatrics to respond somehow to these issues as they relate to children. Those children who have reduced access to preventive medical care suffer the most illness. Poor children have significantly higher rates of a variety of health-related problems, from infant mortality and traumatic death to prematurity (and consequently its related disabilities), failure to thrive, iron deficiency anemia, lead poisoning, perforated appendix, sick days out of school, and hearing loss.[1] The physical, intellectual, and emotional sequelae of these largely preventable conditions can only decrease the chances that these children will work their way out of poverty as adults.

If academic pediatrics has a responsibility to respond to this tragic situation, what should we do? What about staffing clinics in underserved areas? Editors of the American Medical Association and the American Bar Association journals have advocated giving 1 week per year for pro bono service, reminding us of an historic element of professionalism that may have faded in recent years.[2] Certainly, this sort of service can make a major difference in the lives of the children actually treated, and it can be rewarding for the physician. However, to suggest that academic personnel should necessarily contribute even more free medical care, with even further dilution of their academic efforts, seems, in the long run, unwise. Academic departments have special opportunities and faculty with special expertise. These offer the potential to go beyond the immediate problems toward more fundamental solutions with more lasting benefits.

Education is obviously the special province of the academic institution, but what should we teach? The problems are overwhelming, and we have little to offer in the way of solutions; perhaps this is what our students and residents should learn first. It is a widely held tenet of education that the student learns better when knowledge is gained by his or her own initiative and best of all when he or she is truly involved. Involvement in this case necessitates exposure to the societal failures that are related so closely to the poor health of many Americans. This means that students and residents must leave the medical school and hospital and go out into the community where they can see first-hand the consequences of weak education systems, insufficient job training, inadequate low-income housing, the high costs of medical care, and the downward, grinding spiral of poverty. Endorsement

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From the Department of Pediatrics, University of Pennsylvania School of Medicine and The Children's Hospital of Philadelphia.

Reprint requests to the Department of Pediatrics, University of Pennsylvania School of Medicine, The Children's Hospital of Philadelphia, 34th Street and Civic Center Boulevard, Philadelphia, PA 19104 (Dr Johnston).

and collaboration of community leaders are prerequisites. The format might be health promotion and provision of medical care (with faculty) at housing projects, schools, shelters, and clinics within an underserved community, but these activities should be part of an educational program with defined educational goals.

For example, with guidance from pediatric faculty, residents and medical students in Philadelphia have taught health care in inner-city biology classes, conducted perinatal clinics in housing projects, made home visits to adolescent mothers, and assumed responsibility for pediatric care in shelters for homeless or battered women. Participating residents carry a beeper that allows them to offer 24-hour coverage. Teams comprising a resident and one or two medical or nursing students make shelter calls weekly and conduct health fairs at 4- to 6-week intervals to immunize, screen for disease, and educate mothers.

What have the students and residents learned from these experiences? Most respond first that they have gained a "gut feeling" for the broad needs of the mothers and children. The complexity of poverty and the plight of real people elicit frustration, anger, and sadness. A second lesson has been that health is not a survival issue for poor people. When food, clothes, and shelter cannot be assured, baby shots or even treatment for infection or anemia become minor concerns; poor compliance is understood differently. Third, these residents and students have learned the serious handicap imposed by the lack of a record system to track children who have no consistent source of care, no consistent financial aid, and sometimes no consistent parent or caregiver. Three additional lessons have probably been the most important: (1) Most residents report a new recognition of their own limitations in addressing the enormity of the need. (2) Most residents clearly realize that throwing even larger numbers of medical personnel at this problem in efforts like theirs will not make it go away. (3) Finally, often to their surprise, the residents identify a clear need for *research*—research on fundamental causes, on what really works, and even on whether their own efforts have made a lasting impact.

Projects like these, established for the purpose of service and education, may be very important to many individual children, but they do not represent a solution to the fundamental problems; however, they can function as an important means toward that end. Projects like these could serve to recruit the next generation of researchers, teachers, and policymakers, better prepared as a group than their predecessors to formulate meaningful and answerable research questions, to emphasize the importance of disease prevention, and to create public health policies that will work. At the very least, participants will be unlikely to underestimate the magnitude of the problem, and some will become informed and intelligent advocates for change.

How can academic pediatrics work most effectively to achieve fundamental, broad-based solutions? A major part of the answer must lie with research, obviously an essential function of the academic medical center. Basic biomedical research has made tremendous contributions to public health and also, incidentally, to reduced expenditures for the treatment of many diseases.[3] However, there has been too little research conducted regarding possible solutions to the health problems of the poor in America, and an estimated one fifth of our nation's children fall into that socioeconomic class.[4] The critical peer-review system that controls expenditure of public research funds should endorse with enthusiasm good scientific investigation into health promotion and disease prevention. What questions could be more substantial in pediatrics than those related to the reduction of problems such as adolescent pregnancy, premature delivery, adolescent suicide, and accidental deaths?

Research is needed regarding methods to provide care to poor children in our cities and remote rural areas. How can we be more accessible to these children? How can we finance systems to provide this care? How can we reduce medical expenditures in other areas and release funds to meet the need for basic care for poor children? How can we maintain a medical record that will be easily accessible to any pediatrician?

Research into outcomes is needed. Which programs work, and which programs are worth the money and effort? For example, can improved education and counseling reduce prematurity? The fundamental question is whether preventive medicine is cost-effective. Common sense and a quick review of hospital costs suggest that it is, and experience with programs for prenatal care, immunizations, and supplemental food for women, infants, and children (WIC program) support this view.[5,6] However, the content of medical school and residency curricula and the behavior of organized medicine, hospitals, government agencies, and insurance companies reflect little support for such a concept. In their defense, too little scientifically based research has been done in this area to prove that the principle of cost-effective prevention is broadly applicable.

Consider, for example, extracorporeal membrane oxygenation (ECMO) and the problem of nonreimbursed costs for long-term care in nurseries. It is hard to believe that ECMO, employed to save selected neonates, is more cost-effective (much less more humane) than adding equivalent nursing and support personnel to try to prevent unwanted adolescent pregnancy, to help carry pregnancies to term, or to make routine home nurse visits after delivery, which is the standard of care in Britain. Yet more and more hospitals are establishing ECMO programs but not programs to prevent prematurity in the communities they serve. Research is needed.

Research such as that which might compare cost-effectiveness and outcomes of ECMO and preventive care is extremely difficult to conduct, however. Few academic pediatricians have yet had sufficient knowledge, funding, or whatever it takes to try. Although foundations have provided some financial support for such research, too little public money has been available for this purpose compared with the human need, the critical importance of healthy children to the country's future, and the reasonable possibility that research might lead to a reduction in health care costs. The Medical Treatment Effectiveness Program, established in 1989 under the Agency for Health Care Policy and Research, US Public Health Service, may begin to correct this serious deficiency. This program supports research into fundamental issues of health services, such as which treatments actually work best and which are cost-effective. (Inquiries may be addressed to the Agency for Health Care Policy and Research, 18-12 Parklawn Bldg, Rockville, MD 20857.)

Although experimental proof of cost-effectiveness and clinical efficacy is necessary to effect fundamental, broad-based change, provision of the data will not guarantee implementation. Federal and state governments have only recently appropriated enough money to support approximately 60% of those eligible for the women, infants, and children (WIC) supplemental food program, fewer than one sixth of those eligible for Head Start, and about half those who need remedial education, and these programs have been proved to be effective.[7] Expenditures for defense, in the meantime, have far exceeded those for all children's programs combined. Not many pediatricians, either academic or practicing, have had the fortitude to take on the shameful, short-sighted governmental policies that ignore the critical needs of so many of our children. Fortunately, a few have done so, and our professional organizations have begun to guide us toward more effective participation in the area of public policy. Pediatricians are uniquely and eminently qualified to participate effectively by testifying or writing about and by lobbying for legislation related to children.[8] Considering the critical importance of directing public support toward children, serious efforts to accomplish this should be recognized as legitimate academic endeavor, worthy of endorsement by the departmental and medical school promotions committees.

The devastating effect of poverty on the health of so many American children has created opportunities that are as intellectually demanding, emotionally fulfilling, and immediately important as any available in academic pediatrics. The laboratory becomes the community of which the medical school is a part. Which faculty should participate? Not all of them, as the poor are not our only responsibility, but more is needed than we have offered so far, especially with regard to research. No group understands the needs of children better or cares more deeply than do pediatricians. The longer we wait for others to solve the problem, the longer the preventable suffering will continue, the greater the number of children who will sustain permanent injury, and the more profound will be the losses to their future and to ours. Academic pediatrics has a responsibility to use its special talents to address these problems. Those faculty who accept the challenge deserve our highest respect and support.

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Improving Health Care Provision to Neonates in the United States

Mildred T. Stahlman, MD

Any discussion concerning the possible approaches toward improving health care provision to neonates naturally encompasses the improvement of health care provision to their mothers, both before and after delivery. In a larger sense, it encompasses solving the deficiencies in health care provision to the entire population, as babies and their mothers are only two of the overlapping circles in this large Venn diagram.

Thirty-seven million Americans are without health insurance, and therefore frequently without access to necessary care. Simultaneously, we devote a larger portion of our gross domestic product to health care than any other industrialized country, yet we rank 15th in male life expectancy, seventh in female life expectancy, and 19th in infant mortality. There is a national realization, by politicians and the public alike, that health care costs are not only excessively high, but that health care resources are unwisely and inequitably distributed.[1]

A change in perception of the problem is necessary before a solution can be found. We must learn that health, both mental and physical, is a by-product of a national standard of living, which includes adequate housing and nutrition, a meaningful job with reasonable pay scale, a good (we hope excellent) public educational system, and a national economy that does not fluctuate extremely with changes in political leadership. Second, we must admit that despite our high national expenditure on health care, we are unwilling to pay, as a national priority, for equal access and basic care for all, including those who cannot pay.

In days of increasingly restricted federal and state budgets and skyrocketing medical costs, the inevitable questions arise about the direction we should choose (assuming we still have a choice): should we limit our expenditures for tertiary care medicine and opt for better-supported preventive medicine for the majority of patients, or should we continue to support, without regard to the cost-benefit ratio, each new and exciting technological advance, which may be lifesaving for the few who need it but extremely costly for the patient, third-party carriers, and society in general? Nobody wants to make these hard choices, but clearly the time is rapidly coming when someone must. If the medical profession does not choose to participate in this debate, health care planners and politicians will dictate their decisions to us.

I propose that both approaches are desirable, necessary, and, to some extent, affordable if we set our priorities straight. Preventive measures have long-term benefits, with no exciting publicity or dramatic breakthroughs, but, in the long run, they save more lives and prove to be more cost effective than crisis medicine. They require, in a country such as ours with such a wide diversity of health care provisions and patient acceptance, a hard sell from kindergarten onward. It is too late to try to change health patterns in high school, and well nigh impossible in adults with their fixed life-styles. This is especially true in the medically underserved since they are trapped in an environment in which changes in life-style to improve health may be totally unrealistic.

Easily learning new ideas is one of the characteristics of the very young, and the focus on good health patterns must begin then. Successful approaches elsewhere have been to assign each child to the equivalent of a public health nurse, who then knows each child's health problems sequentially and sees to it that parents take advantage of available facilities.

This begins with immunizations and well child care, not with the first major illness. Public television programs are used to promote preventive medicine, often called "social medicine," as the society takes responsibility for its organization and cost. If preventive medicine is begun early in life, a generation of essentially healthy young adults can grow up and, with good health care availability and accessibility ingrained in them, pregnant women can care for themselves and their fetuses from conception onward. This will not be an easy concept to sell, either to the Congress or to neonatal intensive care unit (NICU) physicians, but in the long run it will be seen as a necessity.

If we are to change health care provision to mothers and babies, we must first change their lives. We must educate them to consider health as a goal rather than to expect society to provide crisis care that might have been avoided. One of our major problems is the many medical and social consequences of teenage pregnancy. Unless we can reverse this social trend, high-risk pregnancies and very expensive, very-low-birth-weight infants will continue to consume an inordinate amount of our dwindling health care dollars.

How do we decrease the incidence of teenage pregnancies? First, we must admit the truth about the sexual mores of the young. Ever since the introduction of the birth con-

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From the Department of Pediatrics, Vanderbilt University School of Medicine, Nashville, Tenn.

Reprint requests to the Department of Pediatrics, Vanderbilt University School of Medicine, Nashville, TN 37232-2370 (Dr Stahlman).

trol pill in the early 1960s and the sexual revolution that followed, sexual activity, much of it casual, has been increasing among our teenage population. Unfortunately, we have failed to encourage the use of responsible and effective contraception, and unwanted and high-risk pregnancies and infants have been the consequences of this failure.

Another social result has been the 1½ million abortions performed each year in this country. Until parents, schools, churches, and society in general become realistic about their children's sexual mores and either educate them to different social mores or provide them with the knowledge and means to prevent unwanted pregnancy, abortions, high-risk pregnancies, and low-birth-weight infants will continue to be the result. This lack of responsibility on the part of parents, schools, communities, politicians, and teenagers themselves presents appalling consequences to those whose responsibility it is to provide medical and social care for the tragic outcomes of these failures. We cannot change social mores overnight, but we must begin by telling it like it is. The specter of acquired immunodeficiency syndrome has begun to have an impact on so-called safe sex, but it is ironic that a social good—the prevention of teenage pregnancy—may be a consequence of fear of an international plague!

One of the most pressing current ethical questions in NICUs is that of resuscitating infants of borderline viability. Some would even put it in financial terms. It is an excellent example of expending a large amount of health care resources on a small number of infants who can questionably benefit from them. Should we continue to resuscitate infants born before 25 weeks' gestation and/or whose birth weight is below 500 g? There are those who would put the question at even more mature limits. In contrast to this are some societies in which health care is a priority and prenatal care is provided to all pregnant women early in gestation; in these countries (eg, Sweden), ultrasonography is routinely performed by 16 weeks' gestation and correct dating of almost all pregnancies can be done.

In this country, especially among teenagers, the medically underserved, and the poor, accurate estimation of gestational age is often impossible. Likewise, intrauterine estimates of birth weight are very likely to be overestimates. We then are faced with the terrible decision in the delivery room in cases of fetuses of borderline weight. These infants are almost always in need of some sort of resuscitation, and delay in doing so may affect outcome adversely in very important ways. The decision is frequently the responsibility of a young house officer serving time in a neonatal intensive care unit who may not be prepared by experience or ethical considerations to make such important decisions.

One of our best perinatal centers has taken the position of using constant positive airway pressure (CPAP) and oxygen in the delivery room if needed, and delaying assisted ventilation in most cases of borderline viability until the infant can be carefully assessed with regard to maturity and chances of survivability. If the decision is made to continue the most intensive care, nothing reasonable is withheld until the infant is clearly unsalvageable. If, however, the infant is judged too immature to survive after weighing and careful examination, including functional estimates of maturation, no additional intensive care procedures are carried out. This is a hard line to draw, but some guidelines need to be agreed on since the need to discontinue intensive care, once begun, can be a difficult dilemma to face. We know, based on anatomic and functional evidence, that there is a level of maturation necessary for successful extrauterine life, even when all current technologies are available. Perhaps now is the time for consensus on withholding extraordinary means of life support to the extremely immature but live-born fetus.

The development of regional high-risk perinatal and neonatal care networks during the 1970s was one of the most important concepts leading to improved health care provision to newborns and mothers. It was medically sound and fiscally responsible, as it served to provide the most highly skilled individuals with the most sophisticated (and expensive) technology for high-risk patient care. Most regional centers have had an important educational component, serving to raise the regional hospitals' level of expertise to be commensurate with their facilities and personnel. This system has proved to be cost effective and has been associated with a dramatic lowering of perinatal mortality and morbidity, the byproduct of which has been the survival of infants with lower and lower birth weights.

A new move, called deregionalization by some, has developed in recent years, brought about by an overabundant number of trainees flocking into an exciting new field, the realization by hospital administrators that newborn intensive care *can* be profitable for the hospital, and the willingness of third-party payers to pay both hospitals and physicians for high-risk care. Private hospitals have chosen to leave the network and rely on their own facilities and personnel for this highly visible service. The consequence, in many instances, is the skimming off of paying and insured patients, leaving the regional center, usually a university teaching hospital, to care for the uninsured, the poor, and the highest-risk and most costly patients, socially and medically. No reversal of this trend is foreseeable, and I believe that catastrophic health insurance and some method of limiting the enormous profits from high technology and high-risk care will be the ultimate solution.

When I worked briefly as a cardiologist, I said that I was interested in cardiac success, not cardiac failure. We must be more interested in successful pregnancy outcome than pregnancy failure. Our NICUs are filled with these failures and we tend to focus on them as the exciting problems. However, this excitement generates new ideas and new approaches to patient care, and neonatal/perinatal research has been responsible during the last 30 years for the dramatic changes in survival of the high-risk and very-low-birth-weight newborn. We should not abandon newborn intensive care, but should try to limit our use of technology in place of careful clinical medicine.

Above all, NICUs should be the breeding grounds for bright young investigators who will make the breakthroughs and solve the clinical problems, with basic research followed by carefully designed clinical trials. An interesting suggestion has been made that in times of severe fiscal restraints, such as now, a fixed percentage of the entitlement programs should be set aside for research, much as industry sets aside a fixed percentage of costs for research and development (R. B. Cotton, MD, oral communication, October 1990). Without continuous research, and without a continuous cadre of bright young investigators entering neonatology, we will find ourselves frozen in time with no innovations in patient care in the near future. The by-product of exciting new ideas makes much of the pain, frustration, and cost of intensive care worthwhile.

I am not a medical economist. I was not educated to be one, and the idea of matching the quality of patient care with dollars is abhorrent to me. However, it does not take a financial genius to see the enormous profits that the practice of medicine, the hospitalization of the sick, and the provision of technology and medication can provide to their respective areas of the health care provision system. It has been said that this is the "me" generation, and many physicians have joined those who rank patients' interests below those of first, themselves, the care providers; second, the hospital or academic institution; and finally, third parties (ie, insurance companies, the government, and employers). This attitude is unfortunately becoming increasingly prevalent in maternal and newborn high-risk care.

Third-party reimbursement engendered by procedures and action rather than by thoughtful and responsible inaction has become the norm. The insistence on shorter hours for medical personnel, less personal responsibility, and more consultations, as well as the reliance on technology, the pressures of hospital administrators to fill beds with paying patients, and the enormous markup on pharmaceutical and disposable products, all contribute to enormous patient charges, to less personal satisfaction on the part of care providers, and to more malpractice suits stemming from failures in communication. The result is now he real threat of rationing high-risk (high-cost) care and he development of a two-tiered system of health care provision.

One tier would provide basic, less costly care for the poor and uninsured, and a second tier would provide specialized, more costly care, including all the new technological advances, for the insured and those who can pay. The use of technology has been shown to be directly related to reimbursement for its use.[2] The only redeeming eature of such a two-tiered system besides the expense might be the reemergence of physicians in the first tier who ely on their own skills rather than those of others or on machines and tests. The downside, of course, would be the enormous inequity of accessibility to needed expertise and technology in complicated cases that are unreimbursable.

This two-tiered system is not the answer to the lack of universal health care insurance, and catastrophic health insurance is an imperative. Nowhere is this more apparent than in newborn intensive care. A realistic reassessment of physicians' fees and hospital reimbursement coupled with the need to accept patients on the basis of medical need might even start a trend toward lower charges!

Some corporate participants in the health care provision system, such as for-profit hospitals, pharmaceutical houses, and high-technology equipment manufacturers, and a small percentage of physicians have always been considered to be motivated, at least in part, by greed. Until recently, these were considered the few bad apples in the barrel to be identified and avoided. However, the public's perception has shifted and polls now show that physicians are no longer esteemed above other members of society. Many physicians are considered to not care about their patients' welfare, and medical negligence is the common complaint leading to malpractice litigation.

Communication has broken down between physician and patient, and we have lost our youthful idealism. We, as physicians, are seen as part of the problem of maldistribution of adequate health care, rather than as part of its solution. Darwin taught us that we must change or our species would disappear. Before it is too late, physician, heal thyself.

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Child Abuse and Neglect: Critical First Steps in Response to a National Emergency

The Report of the US Advisory Board on Child Abuse and Neglect

Richard D. Krugman, MD

In June 1990, the US Advisory Board on Child Abuse and Neglect presented its first report to the Secretary of the Department of Health and Human Services and Congress. The board had studied the status of the child protection system (broadly defined as the *system,* not just the child protective services (CPS) agencies involved in the multidisciplinary recognition, intervention, treatment, and prevention of child abuse and neglect). The board was established under provisions of public law 100-294, and the 1988 Amendments to the Child Abuse Prevention and Treatment Act. The mission of the board is to evaluate the nation's efforts to accomplish the purposes of the Act and to make recommendations on ways in which those efforts can be improved.

The board concluded that child abuse and neglect in the United States now represents a national emergency. This conclusion is based on three findings: (1) each year, hundreds of thousands of children are being starved and abandoned, burned and severely beaten, raped and sodomized, berated and belittled; (2) the system created by the nation to respond to child abuse and neglect is failing; and (3) the United States spends billions of dollars on programs that deal with the results of the nation's failure to prevent and treat child abuse and neglect.

The board believes that the extent of the emergency is so compelling that it dictates an immediate response and has recommended 31 critical first steps that will provide a framework for a decade of review and reconstruction of policies and programs that have exacerbated the emergency. These 31 critical first steps, if implemented, will only control the emergency. Once it is brought under control, the board believes that the nation should commit itself to achieving an equally important goal: the replacement of the existing child protection system with a new, national, child-centered, neighborhood-based, child protection strategy. The Board's 31 recommendations (numbered in parentheses below) are organized into the following eight areas.

RECOGNIZING THE NATIONAL EMERGENCY

Each citizen (recommendation 1), each elected official (recommendation 2), and each legislative body (recommendation 3) is called on to recognize the extent of the problem in our society and take personal responsibility to join with others to resolve this emergency.

PROVIDING LEADERSHIP

The president (recommendation 4), the governors of the several states (recommendation 5), the county executives, and mayors (recommendation 6) are called on to become visible and effective leaders within their jurisdiction in renewed child protection efforts. Legislative bodies at all levels are urged to support these efforts by providing funding for the initiatives developed. The rebuilding of our family-support infrastructure is as important as our willingness to rebuild our banking system (recommendation 7). Scientific societies and professional organizations are urged to respond to the emergency by making the issue a priority, stimulating research, and providing guidance to their members (recommendation 8).

COORDINATING EFFORTS

The secretary is called on to work with the governors of the states to eliminate barriers that stand in the way of providing coordinated community services related to the protection of children (recommendation 9), to work with the director of the Office of National Drug Control Policy in the White House to assure coordination of efforts to control substance abuse and child abuse (recommendation 10), and to coordinate with the attorney general to address the issue of fatal child abuse and neglect (recommendation 11).

GENERATING KNOWLEDGE

This area has four recommendations shaped by the board's conviction that good policy begins with good facts. The secretary is asked to establish a federal data collection system that reflects not only social service dimensions of the problem, but the public health, mental health, and legal/judicial dimensions as well (recommendation 12). The secretary is also asked to launch major coordinated initiatives to promote the systematic conduct of research related to abuse and neglect (recommendation 13), to coordinate knowledge about what does and does not work

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From the Department of Pediatrics University of Colorado School of Medicine, Denver, and the C. Henry Kempe National Center for the Prevention of Child Abuse and Neglect, Denver.

Reprint reprints to C. Henry Kempe National Center for the Prevention of Child Abuse and Neglect, 1205 Oneida St, Denver, CO 80220 (Dr Krugman).

in the child protection system (recommendation 14), and to increase the number and professional qualifications of researchers in child abuse and neglect (recommendation 15).

DIFFUSING KNOWLEDGE

The secretary is asked to ensure that practitioners, policy makers, and the general public have ready and continuous access to information through the establishment of a permanent governmental unit (recommendation 16). The board also asks journalists, broadcast executives, publishers, as well as individual media outlets to join in a campaign to promote public understanding of the emergency and the most effective ways of addressing it (recommendation 17).

INCREASING HUMAN RESOURCES

These six recommendations are shaped by the board's conviction that the status, qualifications, training, workload, and representiveness of public agency CPS workers are intrinsic to the crisis in the child protection system. The secretary is asked to establish the position of public agency "CPS caseworker" as a professional specialty (recommendation 18), establish minimum educational requirements for the position of a public agency CPS worker (recommendation 19), and ensure that all public agency CPS workers receive adequate preservice and in-service education and training (recommendation 20). The board proposes that the secretary and Congress, with their counerparts at state and county levels, establish acceptable caseload standards for these workers (recommendation 21). State and local social service officials are asked to aunch an aggressive campaign for recruitment of CPS vorkers representative of the racial, ethnic, and cultural omposition of the caseload population (recommendation 2). The secretary is also asked to ensure a steady increase n the total number of the nation's professionals in medcine, social work, law, law enforcement, mental health, nd education who possess the necessary competence and kill to participate effectively in the protection of children recommendation 23).

PROVIDING AND IMPROVING PROGRAMS

The secretary is asked to ensure that more resources are llocated to establishing voluntary and nonpunitive access help. It should become as easy for a person to pick up he telephone and receive help before abusing a child as is now for a neighbor to report that person after the fact ecommendation 24). The secretary and governors are sked to ensure that efforts to prevent the maltreatment children are substantially increased. At a minimum, this hould involve significant expansion of the availability of ome visitation and follow-up services for all families of ewborns (recommendation 25). Congress and state and cal legislatures are asked to ensure that resources deoted to prevention and to treatment do not come at the pense of each other (recommendation 26). Private sector ganizations are encouraged to increase significantly the volvement of their local affiliates and outlet members or nployees and child protection efforts (recommendation). Congress, the attorney-general, and chief justices are ked to ensure that all state and local courts resolve cases omptly and fairly (recommendation 28). The Secretary Education and his counterparts at the state and local vel are asked to launch a major initiative to establish and strengthen the role of every public and private school in the prevention, identification, and treatment of abuse and neglect (recommendation 29).

PLANNING FOR THE FUTURE

The final two recommendations are shaped by the board's intention to design and propose a new national strategy for the protection of children. The board proposes that Congress direct an appropriate research agency to determine the cost of developing and implementing a comprehensive national program for the prevention and treatment of child abuse and neglect, as well as the projected cost of not developing and implementing such a program (recommendation 30). Finally, the secretary, in concert with the National Governors Association, the US Conference of Mayors, and the National Association of Counties, is asked to develop a model planning process aimed at generating plans for the coordinated comprehensive community-based prevention, identification, and treatment of abuse and neglect with steps taken to ensure that the model process is implemented throughout the nation (recommendation 31).

In presenting these recommendations to the nation, the board has attempted to provide direction, vision, and leadership and expects that its recommendations will serve as the impetus for much needed action to address the national emergency. What does this mean for pediatricians, and why should we care?

Throughout the United States, many pediatricians are faced with a major dilemma; they are knowledgeable about statutes that require them to report all cases of suspected abuse and neglect and yet, in many communities, they observe that their reports are received but inadequately acted on. The child protection system in the United States is fragmented, under-funded, overworked, episodic, and unable to generate any information that would let us know that children are, in fact, being protected. Some physicians have deliberately followed a pattern of civil disobedience and do not report child abuse because of their belief that above all they should "do no harm." In my view, such an approach leaves physicians, and more importantly children, at serious risk. The answer is not to capitulate and abandon a child protection system that is in crisis. As the US Advisory Board suggests, it may be necessary to replace our existing system with one that works, but our efforts need to be focused on rebuilding the supportive infrastructure for families that has been lost in this country (ie, the prevention and treatment arms of the system) without abandoning our recognition and investigation arm. All over the United States, CPS agencies are refusing to open more and more cases so that they will have fewer and fewer with which to deal.

In Colorado, a bill is currently pending in the legislature that would raise the requirements necessary to "prove" a case of abuse from "credible evidence" to "the preponderance of the evidence." The bill will also remove the requirement that home visits be done on all reports, and finally will put in statute that CPS agencies need no longer be involved when children are abused outside the family. This is already happening in practice, but if it becomes the norm nationally to reset in statute those things that we *are* doing instead of those things that we *should* be doing, it is clear that we will continue to erode our ability to protect children. Such statutes are the single best milestones of the decline of a society's moral values.

If children are to be protected and death rates are to decline, we must do more about prevention. Throughout the country, efforts are being made to develop "family reservation programs." These programs, described over 0 years ago by Kempe and colleagues[1] have been rediscovered. They provide intensive 4- to 8-week treatment to amilies to help them out of crises, and have the advantage f leaving children in the home. They are clearly cost effective in that they reduce the need for foster care, but an -week fix for after-the-fact abuse is treatment, not preention, and may be insufficient for long-term success.

It is time for pediatricians in this country to recognize hat our long experiment in making the departments of ocial services in the country responsible for the protection f children has failed. It is not their fault. Beset by budget uts, caught in a web of legal expectations that they could ot possibly fulfill, public child welfare agencies, public ealth nursing, and mental health agencies simply cannot lo what they should be doing. These three critical comonents of the supportive infrastructure that used to care or families have literally disappeared. The role of child velfare is now primarily income maintenance and invesigation of abuse reports. Public health nursing is now prinarily fee for service home health care nursing. The menal health system is completely clogged with the longerm, deinstitutionalized, severely mentally ill. It is no onger possible in this country for a family who needs help *efore* they abuse their child to get that help by calling any f these three agencies. Further, the approach of these gencies is episodic: none has continuity of care as a priniple. It is increasingly difficult in our competitive, prepaid ealth care environment to provide the continuity of care hat these families desperately need, but it is my view that nly the health system has the opportunity to save chillren from the failures of our child protection system.

There are several recommendations within the Advisory oard Report that would form the basis of what pediaricians can do. We need to recognize that this *is* an emerency! We can provide leadership through our profesional societies to ensure that the problems of abuse and eglect will be dealt with as a priority during the coming lecade (not *the* priority, but one of the priorities that we nust pay attention to during this decade). We desperately leed more physicians and child health professionals to vork in both the clinical and research areas of abuse and eglect. We need to take responsibility for prevention. The vork by Gray et al,[2] Olds et al,[3] Helfer,[4] and others has hown that we have the technology to be able to prevent he physical abuse of children. *Not* implementing what we now is tantamount to the withholding of poliovirus vaccine from children when an epidemic is poised to strike.

Pediatricians, through their contact with families, can make a difference. They can develop home visitation systems out of their offices, multispecialty groups, or hospitals that will provide support to new families in their community. Ultimately, if we make it as easy for a family to pick up the telephone and get help *before* they abuse their child as it is now for their neighbors to report them after the abuse has occurred, we will have taken a major step in preventing the abuse and neglect of our children. The Advisory Board's recommendations make it clear that this is no easy task. A future report will outline a new, coordinated, comprehensive, child-centered neighborhood-based child protection system. Pediatricians need to be part of that system so that we can avoid spending millions of dollars on the technology that allows babies born at 28 weeks' gestation to leave the hospital only to go home to an environment in which they are violently shaken or killed within weeks or months of their discharge, or stand by helplessly while millions more go to build prisons that will house the abused children of the 1970s and 1980s who are the failures of our present child protection system.

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Correction

Transposed Wording.

In the article entitled "Lipoprotein Profiles in Hypercholesterolemic Children," published in the February 1991 issue of *AJDC* (1991;145:147-150), an error was made in the "Results" section. On page 148, in the sixth line of the first full paragraph in the left column, triglyceride levels should have read "lower than 1.3 mmol/L" and two lines below, triglyceride levels should have read "higher than 1.3 mmol/L."

Children in and of the Streets

Health, Social Policy, and the Homeless Young

James D. Wright, PhD

The nature of homelessness in the United States was transformed dramatically in the 1980s. Once dominated by older, largely white, broken-down, alcohol-abusive men, today's homeless population contains a sizable fraction of women and children.[1,2] Indeed, women, children, and youth now comprise perhaps three eighths of the total.[3] What are the effects of homelessness on the health and well-being of children? How do these effects compare with those of simply being poor? What are the likely long-term consequences of these effects on the ability of homeless children to mature normally and to achieve productive, independent adult lives? Scholars have been researching these and a range of related questions for the past 10 years, and the results are not encouraging.

That homelessness and extreme destitution exist at all in a society so affluent as ours is shocking. That increasing numbers of the homeless are women, children, and youth—groups that society has traditionally obliged itself to protect—further offends one's sensibilities. It is easy enough (too easy, perhaps) to be indifferent to the plight of Skid Row drunks, but indifference to the circumstances of homeless women and their children requires an unmistakable coldness of heart.

There are many good reasons for the pediatric community to be concerned about the health status of homeless children and youth. Poor physical health and especially chronic physical illness contribute to the cycle of poverty, whereby sick, homeless children of today become the unemployable, destitute, and homeless adults of tomorrow. Recurring health problems of even minimal severity disrupt school attendance and interfere with studying and homework activities. Chronically poor health or physical disabilities will interfere with, if not preclude, normal labor force participation and, with it, the ability to lead an independent adult existence. Thus, poor health is one mechanism by which homelessness reproduces itself in subsequent generations.

Every aspect of a homeless existence compromises physical health to some degree or at least complicates the provision of adequate health services; this is true of both children and adults. Life without shelter corrodes physical well-being in 1000 different ways, most of them too obvious to belabor here. Much that ails children requires little more than a day or two at home in bed—but what if you have neither home nor bed? Nothing is quite so therapeutic to an ailing child as the tender, loving care of a parent. But homelessness is a mean existence in which tenderness, love, and care are often in short supply. Further compounding the difficulties are an often inadequate diet, uncertain sleeping location, limited facilities for daily hygiene, exposure to the elements and to the social environment of the streets, extended periods on one's feet, an absence of support networks to draw on in times of illness, extreme poverty, and on through a long list.[4-8]

Among homeless children and youth in particular, there are additional complications. The shelters for women and children may well present optimal conditions for transmitting the infectious and communicable diseases of childhood.[9] A second problem is that immunization protocols are frequently found to be incomplete or nonexistent[10]; a third is the possibility of widespread physical and sexual abuse. Among homeless teens already out on their own, rates of pregnancy, sexually transmitted diseases, and alcohol and drug abuse and the associated health problems are all inordinately high.[11,12]

Many of the health and nutritional problems of homeless children and youth stem from the extreme poverty of their parents. (The notion that most, many, or even a sizable number of the homeless are "homeless by choice" has been thoroughly discredited by the research of the past decade.[13]) The evident role of poverty in creating homelessness also implies that the recent increases in the numbers of homeless women (and therefore homeless children) are a consequence of the so-called feminization of poverty about which much has recently been written.[14-16] In 1984, approximately two thirds of the nation's poor adults were women[14]; this proportion is increasing. As a consequence, the poverty rate among American children is about twice that of adults. Four of 10 poor people in the United States today are children.[17]

Poverty is a well-known "risk factor" for poor health among children and certainly contributes to the poor health of homeless children. Poverty is strongly correlated with infant mortality in every study that has inquired into the matter, and is also associated with a range of morbidities as well. Homeless children, being poor, must suffer the health consequences of their poverty as well as those resulting from their unsettled living conditions.

Although the effects of poverty on infant mortality are

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From the Department of Sociology, Tulane University, New Orleans, La.

Reprint requests to Department of Sociology, Tulane University, New Orleans, LA 70118 (Dr Wright).

well documented, no study has yet examined the rate of infant mortality among the homeless poor. Among homeless adults, mortality is exceptionally high[8,18]; indeed, the average age at death for various samples of the homeless is reported to be in the range of 50 to 55 years. It is, therefore, a safe bet that homeless infants also die prematurely at a rate substantially higher than average, although, as indicated, this point has yet to be researched.

One mechanism that links poverty to poor health is inadequate nutrition—a problem for poor children in general and the homeless poor in particular. Specific studies of dietary intake or nutritional deficiency disorders among homeless persons, whether child or adult, are relatively rare. Winick[19] has noted that the menu used by the city of New York in its shelters for homeless persons supplies at least one third of the daily requirements for all known nutrients, and is to that extent "sufficient." These diets, however, are typically high in cholesterol, fat, sugar, salt, and starch, so while they may well offer adequate caloric intake, they are far short of optimal. As for the nutrition of those homeless who do not avail themselves of shelters and soup kitchens and who eat mainly what they can scavenge from street sources, nothing further need be said.

A few studies have inquired into the prevalence of nutritional deficiency disorders among homeless children; as would be expected, the rates are high. I[11] reported that 2.2% of homeless children who received care during the first year of the National Health Care for the Homeless program were diagnosed as anemic; this is twice the rate for "normal" children seen in ambulatory pediatric clinics nationwide.[20] An additional 1.6% of the homeless children had nutritional deficiency disorders other than anemia (most of them vitamin deficiency disorders); among children in general, such deficiencies are practically nonexistent (Wright,[11] Table 1). About 2% of the homeless children studied by Miller and Lin[20] were diagnosed as having "growth problems," possibly secondary to dietary insufficiencies, similar to the results reported by Alperstein et al.[10]

General morbidity among homeless children appears to be much more widespread than among children in general or among poor children in particular. Miller and Lin[20] studied 158 homeless children in Seattle, Wash, and reported that "although the majority of the children were considered to be in good or excellent health, the proportion whose health was described as 'fair' or 'poor' was four times higher than in the general US pediatric population."[20(pp671-672)] This study also found a high prevalence of abnormal anthropometry and immunization delays within this population. Homeless children appear to overutilize emergency department services, underutilize preventive health services, and have far fewer dental visits than the general pediatric population. Similar results for homeless children in Boston have been reported by Bassuk et al,[21] and for homeless children in New York by Alperstein et al.[10]

I[11] compared the health problems of homeless children seen in the National Health Care for the Homeless program with those of children included in the National Ambulatory Medical Care Survey. Nearly all disorders are more common among the homeless group. About 7% of the homeless children were found to have scabies and lice infestations, for example, compared with 0.2% of the National Ambulatory Medical Care Survey children; upper respiratory infections were about twice as common, skin disorders four times as common, poor dentition 10 times as common, etc. Homeless children were also more likely than normal children to suffer from chronic physical disorders. Similar patterns were observed among homeless teenagers as well.[12]

Mental health problems of homeless children have been studied in depth by Bassuk et al[21] and Bassuk and Rubin.[22] Depression, developmental delays of varying severity, anxiety, and learning difficulties are reported to be distressingly common. Psychiatric morbidity is also widespread among homeless adults.[23,24]

The general configuration of illness among homeless children is similar to that of children in general. That is to say, the health problems faced by homeless children are not exotic or unusual; they are, rather, the same health problems that all children face. In all studies, by far the most common disorders observed among homeless children are minor upper respiratory infections, followed by minor skin ailments, ear disorders (mostly otitis media), then gastrointestinal problems, trauma, eye disorders, and lice infestations. In most cases, differences in the rates of disorder between homeless boys and girls are reported to be minor.

Differences between homeless children and children in general, in contrast, are often large and in some cases dramatically large. Although the general pattern of illness among homeless children is not atypical of children's illnesses in general, the comparative rates of occurrence are often inordinately elevated.

Children, clearly, are not immune to the deleterious effects of homelessness on physical health. That many of these children are over age 5 years and therefore required to attend school, where their illnesses can then circulate to other children, is an additional point of concern.

It is important to stress here that the best available studies of the effects of poverty on child health report relatively slight differences in the *prevalence* of most disorders between poor and nonpoor children, whether chronic or acute.[25,26] The larger differences are found in the ensuing *consequences* of disease. Differentials on the order of those reported in the studies of homelessness and child health are not to be found anywhere in the published literature on poverty and child health. The evidently disproportionate rate of illness observed among homeless children, in short, is not just a consequence of their impoverished circumstances. Homelessness is an independent and quite consequential risk factor in its own right.

The life chances of homeless children are obviously not bright to begin with. They are saddled first with the burdens of poverty and then with the unique burdens of not having a safe, stable place to live. The effects of homelessness on school performance and intellectual development are now well-known,[22] as are the effects on various physical disorders, both acute and chronic. Among the many good reasons to "do something" about homelessness is that homelessness makes people ill.

These days, the people being made ill by homelessness are increasingly children and youth, who comprise a tenth or more of the total homeless population. To be a poor child is one thing, but to be poor *and* homeless is a thing apart. It is hard to imagine a social environment less conducive to health or normal maturation and development.

Pediatricians at the New York City Children's Health Project have identified what they call the "homeless child syndrome," which comprises "poverty related health problems, immunization delays, untreated or undertreated acute and chronic illnesses, unrecognized disorders, school, behavioral, and psychological problems, child abuse and neglect."[27] It is not true that all homeless children exhibit all aspects of this syndrome. However, most homeless children do exhibit one or more of these problems and disorders; at the very least, they are more commonly observed among homeless children than among children in general or even those at the poverty level.

Knowing how and to what extent homelessness affects the health of children does not in itself tell us what needs to be done. Most of what has been done to date is along the lines of amelioration. There is an evident need to continue such programs: aggressive screening of homeless children for health disorders and proper treatment and health care once problems have been identified. But here, as in many other areas of public health, the only long-term solutions are to be found in prevention. We will avoid the negative consequences of homelessness on the health of children only when we find a way to prevent children from being homeless in the first place.

Sad to say, this obvious truth is much easier to state than to act on. Homelessness is a complex problem rooted in recent trends in the political economy of the nation.[13] A rising poverty rate coupled with a serious and ongoing decline in available low-income housing has served to price an increasingly large segment of the urban poverty population out of the private housing market.[28] Inflation has reduced the purchasing power of Aid to Families with Dependent Children and other welfare programs to the point where the welfare-dependent can no longer maintain stable residences with their monthly payments.[2] In the absence of other sources of support, mothers with children dependent on Aid to Families with Dependent Children find themselves virtually consigned to homelessness in all but the most generous states, unless they are also among those fortunate enough to receive a federal Section Eight housing voucher.

An aggressive, broad-scale federal assault on homelessness in all its various manifestations would easily add several tens of billions of dollars to the annual federal expenditure on housing, health, and human services.[29] No one who has followed the Washington, DC, scene closely for the past few years would consider this the least bit likely anytime in the coming decade. The prospects for community-based local programs are scarcely brighter, since most of the cities and states face budget problems every bit as serious as the federal problem. That would seem to leave the private sector as the most promising source for new programs, but the limit may well have been reached here as well. In fact, approximately three quarters of the total national expenditure for assistance to the homeless already comes from the private sector, principally the churches, and one is entitled to wonder just how much wattage can be cranked from the "thousand points of light." Thus, for the foreseeable future, we will have to content ourselves with programs of amelioration such as those embodied in the Stewart B. McKinney Homeless Assistance Act, knowing full well that such measures do not and cannot provide any final solutions to this problem.

The large number of children now being seen on the streets and in the shelters and other facilities providing services to homeless people means that the homelessness of the 21st century is already being created today. As this is being written, the lives and futures of many tens of thousands of children around the nation are being destroyed by forces over which they have no control. The Children's Defense Fund estimates that "more children die each year from poverty-related causes than traffic fatalities and suicides combined,"[30] and while this is probably an exaggeration, it is nonetheless an exaggeration that makes a point. It is useful, if troubling, to ask, What does the very existence of homeless children say about us as a nation? What image does this present to the world?

In February 1987, I appeared at hearings before the House Select Committee on Children, Youth, and Families to testify to the effects of homelessness on the physical health of children. Among the several witnesses present at the hearings was a lovely 12-year-old Hispanic girl living with her mother and three siblings at one of the large welfare hotels in midtown Manhattan. In the course of her testimony, this young woman remarked, "If I could have anything that I could want, I wish that we could have our own apartment in a nice clean building and a place that I could go outside to play in that is safe. I want that most of all for me and my family." A clean place to live and a safe place to play do not seem like too much to ask. These are not the rapacious demands of some welfare-dependent drug addict, but the plaintive wishes of a young child to have those things that normal children have. As the hearings closed, the thought occurred to me, What kind of world is this, where such simple things can only be a dream to some children? As a kind and generous nation, are we truly prepared to let this continue?

This report has been adapted from a previously published study by Dr Wright.[31]

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A Survey of the Health of Homeless Children in Philadelphia Shelters

Ruth M. Parker, MD; Leslie A. Rescorla, PhD; Jonathan A. Finkelstein, MD; Nathaniel Barnes, MD;
John H. Holmes, MS; Paul D. Stolley, MD, MPH

• We conducted a random-sample survey of homeless children and their mothers residing in Philadelphia (Pa) shelters. One hundred forty-six families were included in the final sample, resulting in an 80% response rate. The aims of the survey were to characterize the child's current and past health status, to determine access to and use of medical services, and to determine the serum erythrocyte protoporphyrin levels and tuberculin skin test status of the children. In addition, psychological tests were administered to both child and parent to assess developmental level and psychological problems. Finally, detailed questions were asked concerning the reasons for the homeless condition. The important reasons for homelessness cited in the survey included physical abuse, substance abuse, disagreements with landlords, and poor living conditions. The children's health problems included a high incidence of reported accidents and injuries, burns, and lead toxicity; the parents suffered from depression, physical abuse, and substance abuse. School-aged children tended to have low scores on tests of expressive vocabulary and word decoding, and preschoolers seemed to be below age expectations in receptive vocabulary and visual motor skills. The findings of this study suggest that homeless children tend to score poorly on developmental and psychological tests and tend to sustain serious burns and accidents. Policy implications of the survey include suggestions for health screening, rehabilitation, and education.

***(AJDC.* 1991;145:520-526)**

Several studies have described the health problems of homeless persons. The health of homeless families and their children is less well defined, but a few studies examining the health status of homeless children are available. Bassuck et al[1] studied 80 families and their 151 children living in 14 Massachusetts shelters in 1985 and reported that about half of the children had developmental lags as assessed by the *Denver Developmental Screening Test.* They also reported a high frequency of learning disabilities, depression, and anxiety. Alperstein et al[2] reviewed clinic records of 256 homeless children younger than age 5 years who attended a primary care clinic in New York, NY. Higher rates of hospitalization, higher serum lead levels, delayed immunization, and increased reports of child abuse were found compared with a population of children of the same age and socioeconomic status who lived at home but attended the same clinic.

A 1986 probability sample of homeless families in King County, Washington, described 82 families with 158 children younger than age 17 years. Thirteen percent of these parents reported their children's health as "fair" or "poor." Compared with the general US population, this sample of homeless persons had a higher rate of emergency department use, and a higher proportion had no health insurance (35% vs 12.5% for the general US population). The population studied was 27% white, 44% black, 8% Hispanic, 6% native American, and 15% mixed. Approximately one third of the children were obese, scoring above the 95th percentile in weight for height measurements.[3]

Comparing 98 children younger than age 12 years residing in New York City welfare hotels with 253 domiciled poor children, Acker et al[4] found an increased rate of iron deficiency among the homeless children.

The *Health Care for the Homeless Project*[5] listed the most common reasons homeless children were brought by their parents to see health care workers: respiratory infection, minor skin problems, ear problems, gastrointestinal complaints, trauma, eye problems, and lice infestations.

PHILADELPHIA SHELTER SYSTEM FOR HOMELESS FAMILIES

Estimates of the composition of the homeless population in Philadelphia were derived from a project directed by the Philadelphia Health Management Corporation, and the 1985 estimates portray a total homeless population in Philadelphia of 10 000 to 13 000 people.[6] At the time of the study, an estimated 2500 to 5000 homeless children lived in Philadelphia, a majority of whom were thought to be younger than age 5 years.

The city shelter network included the one city-owned facility and 22 other privately owned shelters under contract with the city. On presentation to the city authorities, an appropriate space was usually located and the family

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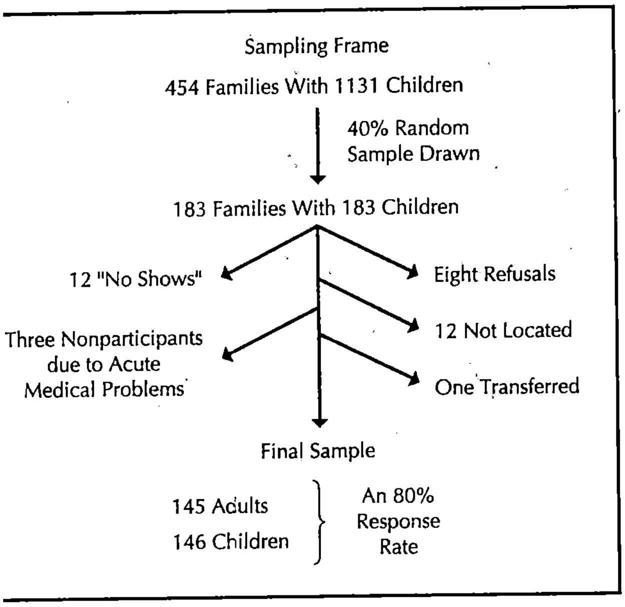
From the Department of Medicine, Emory University School of Medicine, Atlanta, Ga (Dr Parker); the Department of Human Development, Bryn Mawr (Pa) College (Dr Rescorla); the Department of Pediatrics, Children's Hospital, Boston, Mass (Dr Finkelstein); the Department of Urology, Duke University Medical Center, Durham, NC (Dr Barnes); and the Clinical Epidemiology Unit, Section of General Internal Medicine, Department of Medicine, University of Pennsylvania School of Medicine, Philadelphia (Mr Holmes and Dr Stolley).

Reprint requests to Emory University School of Medicine, Department of Medicine, 69 Butler St SE, Atlanta, GA 30345 (Dr Parker).



agrammatic representation of sample and final response rate.

as placed within a few hours; however, if an appropriate iit could not be found, the family was housed in a large mnasiumlike room at the city-owned facility, which ac- mmodated as many as 75 families.

All of the 22 shelter buildings in our sample were struc- res converted from former uses, ie, a car dealership, a tirement home, an orphanage, a funeral home, and a hool. The capacity of the shelters and the actual living rangements for families varied greatly, with from one to x families housed in one room. Few cribs were available d only one shelter had an isolation room for persons ith communicable diseases. All of the shelters housed ngle women with dependent children, and four of the elters also housed single women without children. One elter housed a large proportion of troubled girls placed ere for supervision and guardianship.

Most shelters referred their clients to local neighbor- ood clinics or hospitals for medical assistance. One shel- r had a nurse and an infirmary, and another shelter em- loyed the services of a visiting nurse practitioner rganization. All shelters had paid staff, including night- me staff. Three privately owned shelters were managed y formerly homeless women who resided there.

AIMS AND OBJECTIVES

When we planned our study in September 1987, there ras little published information concerning the health sta- s of homeless families, and much of what was available ad not been obtained using random sampling methods. Ve therefore designed a survey of homeless families re- iding in shelters in Philadelphia to obtain descriptive in- rmation that would be helpful in health planning and in lentifying specific problems and unmet health needs. In urveying randomly selected homeless families in Phila- elphia shelters to describe their health status and other haracteristics, we targeted seven main areas: (1) the hild's health, including general health perceptions, med- al history, and recent illnesses; (2) access to health ser- ices for children; (3) social, economic, and demographic eatures of the family, such as family structure, income, vork history, and school performance; (4) parental health istory, which focused on drug and alcohol use, chronic llnesses, and childbearing history; (5) visual screening of he children; (6) laboratory investigation of the children using a tine test for tuberculosis and determination of erythrocyte protoporphyrin (EP) levels; and (7) developmental and psychological screening of the children using tests appropriate to their ages. By obtaining such information we hoped to better understand how resources can be best allocated to the homeless population.

SUBJECTS AND METHODS

Defining the Population and the Sampling Method

After receiving permission from the Philadelphia government to conduct the study, we obtained information regarding the number, type, and location of all shelters with which the city contracts. We excluded homeless families residing at noncontracting shelters since there was no available list of all such facilities and they housed only a small proportion of the city's homeless families. We contacted each of the 21 privately owned shelters and the one city-owned facility to request their participation in our study and to ascertain their current occupancy. Two shelters, each housing about 20 families, refused to participate; seven shelters had only one to eight families present and were excluded from our sampling frame due to their small size. Because homeless families were randomly assigned to shelters regardless of shelter size, the exclusion of these nonparticipating shelters was unlikely to have biased our sample. The remaining 13 shelters agreed to participate. We conducted on-site visits to interview shelter directors and conduct the survey.

Our research team spent prearranged days at each shelter conducting the survey. Each shelter maintained a roster of resident families. Using a table of random numbers, we selected from 28% to 49% of the families present at each shelter for study. The family was contacted at least twice to set up an appointment. Next, we randomly selected one child, aged 12 years or younger, from each family and invited this child to participate in the study. There were 454 families, with 1131 children, in the 13 shelters during our census. One hundred eighty-three families, with one randomly selected child per family, were selected for study. One hundred forty-six families enrolled in the study. There were 37 nonrespondents, including eight who refused to participate, 12 who did not show up for interviews, 12 who could not be located to request participation on at least two attempts, three who could not participate due to acute medical problems (ie, premature labor for one woman and bleeding during pregnancy for two women), one who was transferred to another shelter before her scheduled appointment, and one who was inebriated on the two occasions we arranged for the interview. The mother's responses in this latter case were not included in our analysis, but those of her child were included.

The study included information on 145 families and 146 children (Figure). Psychometric data were requested only for the 98 children aged 2 years and older. Following completion of this study of homeless children, we were able to collect psychometric data on a small sample of inner-city–domiciled children in Philadelphia. These comparative data are reported elsewhere.[7]

Parents signed informed consent forms, and an oral interview was conducted lasting 45 minutes. The survey questionnaire targeted four main areas: (1) demographic and socioeconomic characteristics, including family structure, a calendar of homelessness (a chronological list of all places the family resided in the previous 5 years), and use of social services; (2) access to medical care; (3) the child's health history, including perceptions of general health, functional status, chronic medical conditions, hospitalizations, immunization status, and school performance; and (4) parental health history, including chronic and recent acute illnesses, history of smoking, and alcohol and drug use.

Adult subjects completed the Peabody Picture Vocabulary Test-Revised (PPVT-R), Beck Depression Inventory (BDI), and an age-appropriate Achenbach Child Behavior Checklist (CBCL). Simultaneously, the children completed a battery of age-appropriate psychological and developmental tests, listed and described below.

Tests Administered

Wechsler Intelligence Scale for Children-Revised (WISC-R) Vocabulary.—The best predictor of WISC-R IQ, this subtest involves asking the child to give definitions for a list of vocabulary

Table 1.—Highest Level of Education Achieved by Homeless Mothers (N=145)

Education Level	No. (%) of Mothers
<12 years of school	72 (50)
<12 years and vocational school	2 (1)
High school equivalence degree	5 (3)
High school graduate	38 (26)
High school graduate and vocational school	18 (12)
Some college	10 (7)
College graduate	0

Table 2.—Parity of Homeless Mothers (N=145)

No. of Children	No. (%) of Mothers	Cumulative %
1	22 (15)	15
2	35 (24)	39
3	44 (30)	69
4	20 (14)	83
5	9 (6)	89
6	8 (6)	95
7	2 (1)	96
8	3 (2)	98
9	2 (1)	99

words. The test was given to children aged 6 to 12 years to measure verbal ability.

WISC-R Block Design.—The child assembles geometric blocks to duplicate a model under a time limit. Block Design is the subtest correlating most highly with WISC-R Performance Scale IQ, and was given to children aged 6 to 12 years.

Wide Range Achievement Test–Revised (WRAT-R) Reading.—On this subtest, the children aged 6 to 12 years were asked to read a list of words. Children who could not read were asked to match and identify letters of the alphabet.

House-Tree-Person (HTP).—The child is asked to draw a picture of a house, a tree, and a person and then to answer a few questions about each drawing. The drawing of a person was scored by certified school psychologists using the Goodenough-Harris developmental system.

Stanford-Binet Intelligence Scale: Fourth Edition (IV) Vocabulary.—This subtest assesses a child's ability to label pictures and give word definitions for common words. The vocabulary subtest is the best predictor of overall Stanford-Binet IV Test Composite Score (IQ) and was given to children aged 2 to 5 years.

PPVT-R.—This test was given to children aged 3 to 5 years to assess their receptive vocabulary by asking them to point to one of four pictures on a page that depicts the stimulus word.

Beery Visual-Motor Integration (VMI).—The Beery VMI Test involves copying a series of simple geometric forms (eg, line, circle, and cross) and was given to children aged 3 to 5 years.

Yale Cubes.—Children aged 2 to 5 years were asked to copy a series of cube formations (ie, tower, bridge, house, and steps). This task was drawn from the Gesell Preschool Screening Test and the Yale Developmental Schedules.

Yale Drawings.—Two-year-old children were asked to copy a set of geometric forms (ie, vertical line, horizontal line, cross, and circle).

CBCL.—Mothers of all the children completed the CBCL. This involved reading a list of 118 behavioral symptoms and indicating for each one whether it was "untrue," "somewhat true," or "very true" of her child. The scores for "Total Problems," "Externalizing," and "Internalizing" were calculated for each child.

BDI.—A questionnaire for adults (mothers in this study) was administered that measures the presence and degree of "depression" or depressive affect.

Table 3.—Maternal Age at Delivery of First Child (N=145)

Maternal Age, y	No. (%) of Mothers	Cumulative %
13	1 (1)	1
14	6 (4)	5
15	13 (9)	14
16	21 (14)	28
17	20 (14)	42
18	25 (17)	59
19	14 (10)	69
20	14 (10)	79
≥21	31 (21)	100

Table 4.—Incidence of Illness Among Homeless Children During Previous 4 Weeks (N=145)

Type of Illness	No. (%) of Children
Gastrointestinal	54 (37)
Cough with fever	35 (24)
Ear infection	29 (20)
Conjunctivitis	25 (17)
Other	2 (1)

Three Wishes.—Each child was asked to tell three things he or she would wish for if wishes could come true.

Children older than age 6 years had their vision screened using the Richmond Kindergarten Test Chart.

Parents gave separate informed consent for laboratory testing of their children. These tests included a tine test placed on the right forearm by a standard procedure (read by an interviewer 48 to 72 hours later) and a determination of the EP level from a finger stick sample of blood to assess lead exposure. The EP level was determined by the City of Philadelphia Health Department Laboratory. Values greater than 0.62 μmol/L were considered abnormal, and a follow-up determination of serum levels was requested. Parents were notified of abnormal EP levels and instructed on the proper follow-up procedures.

RESULTS

Population Studied

Adults.—One hundred forty-five adults completed our interview and examination. One hundred thirty-one subjects (90%) were black, 11 (8%) were white, and three (2%) were white or Hispanic. Fifteen percent stated that they were currently married and 46% were "never married"; the remainder said they were divorced or separated. Half of these 145 adult respondents had not completed high school; 10 (7%) of the participants in the study stated that they had completed at least 1 year of college (Table 1).

Concerning parity, 44 (30%) of the 145 respondents reported that they had three or more living children, and two individuals (1%) reported that they had nine children (Table 2). Eighty six (59%) of the respondents had delivered their first child by age 18 years (Table 3). One-hundred forty (97%) of the 145 mothers stated that they were not working; only five (3%) were currently engaged in some part-time work.

Although the mean length of stay in the current shelter was 12.7 weeks, the range was wide (<1 week to 82 weeks), and the mean length of homelessness was 19.3 weeks. Families had resided in a mean of 3.2 places (range, one to 20 places) in the previous 12 months, and in the previous 5 years had moved a mean of 4.7 times (range, one to 22 times). In the previous year, 14 (10%) owned their

Table 5.—Incidence of Major Accidents, Injuries, or Medical Conditions Over the Lifetime of Homeless Children (N=145)

Condition	No. (%) of Children
Burn with scar formation	20 (14)
Lead poisoning	16 (11)
Poison/pill ingestion	10 (7)
Fracture	9 (6)
Unconsciousness	9 (6)
Seizure	6 (4)

Table 6.—Reasons for the Hospitalization of Homeless Children in the Previous Year (N=145)

Reason for Hospitalization	No. (%) of Children Hospitalized
Injury	12 (8)
Other illness	12 (8)
Asthma	7 (5)
Dehydration	6 (4)
Seizure disorder	4 (3)
Respiratory infection	3 (2)
Other infection	3 (2)

Table 7.—Chronic Illnesses of Homeless Mothers Requiring Regular Medical Care (N=145)

Illness	No. (%) of Mothers
Hypertension	13 (9)
Renal disease	6 (4)
Cardiovascular disorder	5 (3)
Diabetes mellitus	4 (3)
Cancer	3 (2)
Physical disability	6 (4)
Other	23 (16)

Table 8.—Drug Use Reported by Homeless Mothers in the Previous Year (N=145)

Type of Drug	No. (%) of Mothers
Marijuana	61 (42)
Cocaine ("crack")	32 (22)
Amphetamines	4 (3)
Polychlorinated biphenyl	4 (3)
None	44 (30)

own homes, 112 (77%) rented their own apartments, 72 (50%) lived with their mothers, 78 (54%) "doubled up" or shared housing, and 10 (7%) lived on the streets, in abandoned buildings, or in cars. (This total is greater than 100% because more than one living arrangement was possible during the year.)

When asked about their *primary* reason for homelessness, 36 (25%) cited poor living conditions at a previous residence; 33 (23%) were evicted; 29 (20%) had disagreements with their landlord, other tenants, or family members; 15 (10%) attributed their homelessness to a lack of money or loss of a job; 10 (7%) had experienced a disaster (eg, fire or flood); seven (5%) cited abuse, and four (3%) cited divorce or separaton.

Findings Concerning General Health and Use of Services

When queried about their child's health, 55 (38%) of the respondents believed it was "excellent"; 39 (27%), "very good"; 29 (20%), "good"; 19 (13%), "fair"; and only three (2%) thought that their child's health was "poor." This favorable assessment of their children's health was restated when the parents were asked to compare the health of their child with that of other children; very few stated that their child's health was worse than that of most other children. Furthermore, only nine (6%) of 145 parents said that their child had a condition that interfered with usual activities.

When mothers were asked about recent health problems their child had encountered in the previous 4 weeks, gastroenteritis, otitis, cough, and conjunctivitis were the conditions most frequently mentioned (Table 4). Twenty-nine (20%) of the 145 respondents for these questions reported that their child had been seen in an emergency department during the past year as a result of an injury or fall, and nine (6%) of these children had sustained a fracture; nine children (6%) were reported "knocked unconscious" because of trauma during the previous year. Twenty (14%) of the 145 children had received burns during the previous year severe enough to have scarred; 10 children (7%) had swallowed a poison or medicine and required emergency treatment (Table 5).

Seventeen of the children (12%) had been hospitalized during the previous year; the major reasons for hospitalization included injury, seizures, dehydration, asthma, and other respiratory infections (Table 6).

The mothers of the homeless children were asked about the antenatal care they received when pregnant with the child in question: only four (4%) of the 104 mothers who answered this question reported receiving no care at all, and most of the other respondents reported first receiving care during their first trimester. Fourteen (13%) said that their care began during the fifth month of pregnancy or later.

By and large, parents seemed to have found some sort of medical care for themselves and their child; however, 23 (19%) of 124 respondents could not identify a place to which they could go for care. Fifty-five (44%) used the hospital emergency department or clinics for care, 53 (43%) went to a community clinic, 12 (10%) went to a private physician's office, and only four (3%) visited a health maintenance organization.

Dental care was harder to evaluate since many of the children were aged 3 years or younger, an age group that usually does not receive regular dental care.

Findings of Physical and Laboratory Examinations

Tine tests to screen for tuberculosis were placed on 92 children. Interviewers read the results between 48 and 72 hours later and found six positive findings (7%) from 0 to 5 mm, one positive finding (1%) from 6 to 10 mm, and 69 negative findings (75%). We were unable to locate 16 children (17%) for the test reading. Finger-stick blood samples for EP determination by extraction were obtained from 96 children, but 20 samples were not processed because of clotting or insufficient quantity. Nine (12%) of the remaining 76 samples had abnormal values (>35 µg/dL).

Visual acuity of children older than age 6 years was checked using the Richmond Kindergarten Test Chart. Ten (26%) of the 39 children tested failed to identify pictures at a distance of 600 cm with visual acuity better than 20/40.

Table 9.—Descriptive Statistics for Psychometric Measures

			Mean (SD)				
Measure*	**Age Range, y**	**Domain**	**Normative**	**School-Aged (6-12 y) (n=43)**	**Preschool (Aged 3-5 y) (n=40)**	**Toddlers (Aged 2 y) (n=15)**	**Mothers (n=145)**
WISC-R Vocabulary	6-12	Verbal ability	10 (3)	6.67 (2.92)	. . .	. . .	. . .
WISC-R Block Design	6-12	Nonverbal problem solving	10 (3)	7.72 (3.33)	. . .	. . .	. . .
WRAT-R Reading	6-12	Reading, decoding	100 (15)	80.88 (20.81)	. . .	. . .	. . .
Draw-A-Person	3-12	Visual-motor skill	100 (15)	85.50 (16.22)	79.96 (13.12)	. . .	. . .
Binet IV Vocabulary	2-5	Verbal ability	50 (8)	. . .	41.44 (4.25)	45.27 (2.97)	. . .
PPVT-R	3-5, Mothers	Receptive vocabulary	100 (15)	. . .	67.84 (13.89)	. . .	71.99 (14.48)
Beery VMI	3-5	Visual-motor skill	100†	. . .	82.46 (9.06)	. . .	. . .
Yale Cubes	2-5	Nonverbal problem solving	100†	. . .	85.41 (21.43)	87.13 (11.72)	. . .
Yale Drawings	2	Visual motor skill	100†	. . .	. . .	88.67 (32.28)	. . .
CBCL Internalizing	2-12	Emotional problems	50 (10)	57.02 (9.11)	59.05 (11.61)	47.00 (6.98)	. . .
CBCL Externalizing	2-12	Behavior problems	50 (10)	57.68 (11.49)	55.05 (9.56)	45.13 (7.90)	. . .
CBCL Total Problems	2-12	Overall problems	50 (10)	57.92 (10.42)	59.87 (11.08)	44.73 (8.06)	. . .
Beck Depression Inventory	Mothers	Depression	. . .	. . .	. . .	. . .	13.26 (10.28)

*WISC-R indicates Wechsler Intelligence Scale for Children-Revised; WRAT-R, Wide Range Achievement Test–Revised; PPVT-R, Peabody Picture Vocabulary Test–Revised; Beery VMI, Beery Visual-Motor Integration; and CBCL, Child Behavior Checklist.

†Quotients produced by dividing mental age by chronological age.

Health of Parents

The reported health status of the mothers is summarized in Table 7. Seventeen (12%) of the 138 respondents stated that they were pregnant at the time of the interview. Ninety-nine (68%) of 145 mothers rated their own health as "good" or better, but specific health problems were cited by many women. Six (4%) of 145 respondents reported physical disabilities that interfered with their daily activities, and 13 (9%) reported that they had hypertension. Twenty-one respondents (14%) reported having been hospitalized in the previous year for a reason other than childbirth. While most respondents felt their health was "adequate," a significant number had conditions that required short- or long-term medical care, and this may have contributed to their difficulties in finding employment, housing, and child care.

The incidence of emotional difficulties severe enough to cause the mother to consult a psychiatrist, counselor, or therapist in the preceding 6 months was 14% (20 respondents), and seven mothers (5%) reported having been hospitalized at some time in their lives specifically for mental illness.

The prevalence of *reported* alcohol use was surprisingly low, with 102 (70%) of the 145 women stating that they consumed less than one alcoholic drink per day, and only four (3%) stating that their alcohol use had contributed, even slightly, to their present circumstances. Seventeen (12%) reported that alcohol use by others in their household was "a big part" or "the main cause" of their present problems. Thirteen women (9%) reported that their own drug use was "a big part" or "the main cause" of their present problems; 26 (18%) reported that drug use by others had created a significant problem for them. Table 8 shows the number of respondents who used specific drugs during the previous year.

Finally, thirty-one women (21%) reported having been battered or physically abused in the preceding 12 months, while only four (3%) reported that their children had been physically abused in the preceding year.

The estimates of the incidence and prevalence of these health and substance use problems may be falsely low because of underreporting. It is possible, for instance, that the clients perceived that admitting to some of these problems might cause them to be forced out of the shelter, despite our guarantees of confidentiality.

These women appeared to have the range of health problems found in the general population of women in this age group. However, the number who became pregnant as teenagers, who had been recently battered, and who cited drugs as a major cause of their difficulties was impressive, although we have no control group with which to compare the data.

Psychometric Data on School-Aged Children

Descriptive statistics for the psychometric data for the 6- to 12-year-old children appear in Table 9. These 43 children scored significantly below average in WISC-R Vocabulary and Block Design tests. However, these scores were within the range of scores obtained by black children whose parents are in the lowest occupational category of the WISC-R standardization sample.[8]

The mean score for this group of children aged 6 to 12 years on the Goodenough-Harris scoring of Draw-A-Person (DAP) was 85.5, indicating performance about one SD below average. Only 28% of the children scored in the average range or higher on the human figure drawing.

The mean score on the reading subtest of the WRAT-R for these 43 children was 80.9, or more than one SD below the mean for the standardization sample. Only one third of the children were reading at age level. This is consistent with the fact that only 25 (63%) of 40 children were in the correct grade for their age. However, it is somewhat inconsistent with the mothers' reports that 19 (48%) of 40 children had "good" or "excellent" performance in school, 11 (28%) had "average performance," and only 10 (25%) performed "below average" or were not attending school. School information was not obtained for three of the 43 school-aged children.

Absence from school was a major problem for these homeless children: 12 (30%) of 40 had missed 10 or more days of school in the past 2 months and another eight (20%) had missed between 5 and 9 days.

Psychometric Data on Preschool Children

Table 9 presents the scores on the Binet IV Vocabulary subtest, which measures expressive vocabulary performance. These 40 homeless preschool children scored about 1 SD below the mean for the general population. The children performed even more poorly in the PPVT-R, the test of receptive vocabulary; their mean score of 67.8 was more than two SDs below the mean for the general population. This was comparable with the performance of their mothers, who obtained a mean PPVT-R score of 72.0, indicating extremely poor receptive vocabulary skills.

The 40 preschool children scored below age level on the Yale Cubes, with a mean score of 85.6. These preschool children obtained a mean score of 82.5 on the VMI, indicating below-average performance on design copying. Visual motor immaturity was also shown on the DAP test, in which the mean score (based on the Goodenough-Harris norms) was 79.7; however, only 26 (65%) of 40 of the 3- to 5-year-olds were able to draw anything even "scorable" on the DAP.

Psychometric Data on 2-Year-Old Children

Few 2-year-olds were tested; their mean score on the Binet IV Vocabulary was 45.3, which is within one SD of the population mean. These 2-year-olds performed somewhat below age level on the Yale Cubes, with a mean score of 87.1. Their visual-motor skills were examined with the Yale drawings. Based on a ratio score using developmental age, these children scored slightly below average for their ages (88.7).

Behavioral-Emotional Adjustment of All Age Groups

The mother of each child aged 2 years and older completed the CBCL. Research has demonstrated that differences by social and economic group are minimal on this measure.[9] Maternal reports on the CBCL for school-aged and preschool children yielded mean scores close to the population mean; CBCL scores for the 2-year-olds were slightly below the mean (Table 9). Four (9%) of the 43 older children had scores above 70, or in the "clinical range," while seven children had scores between 65 and 70 for "Total Problems." Eight (20%) of 40 preschoolers had "Total Problems" scores in the "clinical range." No 2-year-olds were reported to score in the "clinical range" for "Total Problems," "Internalizing," or "Externalizing." On average, they did not show more emotional or behavioral symptoms than 2-year-olds in the CBCL standardization sample.[10]

These 145 homeless mothers reported substantial depression, according to the Beck Depression Inventory.[11] Although 69 (48%) scored in the normal range, 38 (26%) scored in the mild-to-moderate range, and 38 (26%) scored in the moderate-to-severe range of depression.

Clinical Measures: Three Wishes and HTP Drawings

The school-aged children showed a strong tendency to wish for major changes in their life situation, indicating an intense awareness of their plight as homeless poor people. Thirteen (48%) of the 27 older boys and eight (50%) of the 16 older girls made at least one wish to be out of the shelter or to have a new house. Fourteen (33%) of the 43 older boys and girls wished for money. Four (25%) of the 16 older girls wished for the family to be together and healthy, and 10 (37%) of the 27 boys wished for a car. In contrast, only 11 (28%) of the 40 younger children wished for these major life-style changes affecting the family. Rather, preschoolers showed a strong tendency to wish for more immediate personal pleasures: 11 (85%) of the 13 younger boys and 12 (44%) of the 27 younger girls wished for toys. Only younger children used their wishes for miscellaneous or minor objects. Thirty one percent of older girls (five girls) and younger boys (four boys) wished for fulfillment of "dreams," such as to be a princess, to be a flower, to visit Disney World, to be a "man," or to "do anything I want."

The older children's drawings of houses were remarkable as expressions of their wish for a comfortable and well-appointed home. Embellishments such as curtains, flower pots, "welcome" signs, and decorative details were common. The children's comments explicitly and poignantly expressed their unhappiness at being homeless and their desire for an inviting house in which to live.

COMMENT

This 1988 survey of homeless families residing in Philadelphia shelters revealed some results that were expected and some that were surprising. Unlike many previous studies of this population, selection of participants was random and should therefore be representative of Philadelphia's homeless population at that time. Because this was a field study, the conditions of data collection were suboptimal. There was often no appropriate area to interview parents or test children. Technical problems (20 of 96 blood specimens clotted before reaching the laboratory) and probable underreporting, especially on issues of drug use and physical abuse, may have hampered data interpretation. A comprehensive assessment of causes and consequences of homelessness would require comparative sampling, which was beyond the scope of this project. Thus, our analysis was limited to descriptive statistics.

The homeless parents interviewed most commonly cited poor living conditions, eviction, or disagreement with a landlord as their primary reasons for homelessness. Thirty-nine (27%) described illegal drug use by themselves or other household members as a major contributor to their current problems. Our overall impression was that the majority of these families lived in marginal situations (ie, doubled up, overcrowded, and/or unsafe), until some recent event (ie, argument, abuse, drug problem, pregnancy, or birth of a baby) forced them to leave. Many families described "choosing" to enter the shelter system as a better alternative than their current housing arrangements.

The children's reported health problems were those most prevalent at this socioeconomic level. Injuries and accidents were commonly reported, as were communicable diseases, such as gastroenteritis and upper respiratory infections. Nine (12%) of 76 children had abnormally high free EP levels. We do not know what proportion of these results represents lead intoxication or anemia from iron deficiency or other causes. However, parents reported that 16 (11%) of 145 children had been diagnosed as having lead poisoning in the previous year.

Despite the health problems described by parents, most believed that their children were in good or excellent health. Although most families could identify a source of care, almost half named a hospital emergency department or clinic rather than local health centers or individual practitioners.

The homeless mothers had a high degree of parity and, on average, had delivered their first children while teenagers. Their level of schooling was low and they performed poorly on a test of receptive vocabulary. They tended to suffer from depression, and many reported being abused by husbands or male companions. In addition to self-reported emotional difficulties requiring recent hospitalization, many mothers reported significant chronic medical problems.

The children had poor school attendance records and scored poorly on intelligence tests and receptive vocabulary tests, as well as having impaired ability to perform visual-motor skills. The older children expressed yearnings for a stable family structure, a desire to leave the shelter, and hope to have a home.

The problems of the homeless are protean and complex, just as the causes are multifactorial. The shelter system, created to supply emergency and temporary housing, is often the residence for homeless persons for prolonged periods. The health of the resident mothers was characterized by depression and multiparity as well as the presence of serious psychiatric and medical illnesses for some. The resident children tended to suffer serious injuries, such as burns, and many may have had anemia and/or high blood lead levels. The children scored poorly on developmental and psychological tests.

Some of the problems of homeless persons living in shelters that need to be addressed include lead toxicity, anemia, and accidents of children, as well as substance abuse and physical abuse of mothers. The psychological and developmental needs of homeless children may require special programs if these deficits are to be overcome.

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Pediatric Acquired Immunodeficiency Syndrome, Poverty, and National Priorities

Margaret C. Heagarty, MD

Human immunodeficiency virus (HIV) infection or acquired immunodeficiency syndrome (AIDS), as found in children, represents a microcosm of the problems and failures of this nation's health care system for the poor.

EPIDEMIOLOGY

When Oleske et al[1] and Rubenstein et al[2] first described the disease in children, it was not evident that AIDS was to become a disease found predominantly in poor children of minority status. But in the years since those first reports appeared, epidemiologic studies have demonstrated that AIDS in children is largely acquired through perinatal transmission from HIV-infected mothers who are or have been involved in intravenous drug use or who have had intercourse with someone involved in the drug culture. About 15% of children with AIDS are hemophiliacs or others who were infected by contaminated blood products before the advent of the national universal HIV blood screening program. Presumably, the number of transfusion-related cases will decrease with time.

To date, children with AIDS have been found in most urban areas of the country, but the disease continues to cluster in three distinct geographic areas: low-income areas of New York City, Northern New Jersey, and Miami, Fla. Those who live in these disadvantaged communities are of either African American or Hispanic origin; 53.4% of children with AIDS are from New York, New Jersey, or Florida, and 77.5% are of either Hispanic or African American ethnicity.[3] Since many are children of intravenous drug-using parents, some of whom have AIDS themselves, they and their parents live on the fringes of their disadvantaged communities, often isolated from their larger families or from other social supports that might be more easily mobilized for other, more advantaged groups with such a serious, lethal disease. In short, most children with AIDS and their families come largely from the most socially disorganized, economically deprived segments of our society.

PROGNOSIS

During the recent past, the prognosis for children with AIDS has improved for two reasons. First, pediatricians in areas in which the disease is prevalent have become more experienced in its early diagnosis and in the use of vigorous antibiotic therapy for bacterial infections to which these children are particularly prone. Second, research and development of scientific antiviral therapy for children, which, at times, has seemed too slow and too little, has finally become available in most areas in which significant numbers of children with the disease are found. While much more research is required before we fully understand AIDS and therefore its medical treatment, by now, some 10 years into the AIDS epidemic, the prognosis for children with AIDS has improved. Nevertheless, these children and their families face a complicated, chronic disease with a very guarded prognosis.

MEDICAL CARE SYSTEM

Because these children and their families are poor, they must also face a system that at times seems designed to impede rather than facilitate the provision of medical care. During the past 40 or more years, local and federal governments have developed a series of social and financial supports for the poor. However, the statutory and regulatory requirements of these programs are so complex, dysfunctional, fragmented, and disorganized that professionals providing care for these families often spend as much or more time dealing with a variety of local, state, and federal governmental bureaucracies as they do providing direct medical care or social support. In our zeal to make absolutely certain that no rascals or scoundrels get something to which we judge they are not entitled, we have constructed paper edifices and barriers that no one could easily master. We wonder why the most socially disorganized and disadvantaged members of our communities have trouble "getting on Medicaid" or registering for this or that social program. Indeed, we sometimes blame them, call them unmotivated, noncompliant, or worse. Since I have an acute anxiety attack when facing a Bureau of Motor Vehicles for a driver's license, I suspect that I, and probably most of us, would decompensate entirely if we had AIDS and had to try to qualify for Medicaid or Social Security benefits.

Finally, more than half the cases of AIDS reported to the Centers for Disease Control, Atlanta, Ga, have come from only 15 cities in this nation. Because our major urban disadvantaged communities contain large numbers of intravenous drug users and because HIV is transmitted via the shared needles of intravenous drug users, the prevalence of HIV infection in these communities is very high. This increased prevalence of the infection has led to rapid

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From the Department of Pediatrics, Harlem Hospital Center, and the College of Physicians and Surgeons of Columbia University, New York, NY.

Reprint requests to Harlem Hospital Center, Department of Pediatrics, 506 Lenox Ave, New York, NY 10037 (Dr Heagarty).

spread, not only among the intravenous drug–using population, but also by heterosexual contact among adults who do not use drugs. It is not uncommon to make the diagnosis of AIDS in a child of a woman who is not a drug user and who is completely unaware that she has acquired the HIV infection from an infected sexual partner.

Because AIDS in children is a disease of the urban poor, the public general hospitals in our major cities provide much, if not most, of their medical care. In the best of times, these city or county hospitals are underfinanced, embattled medical care institutions of last resort. Historically, they have survived in a financial hand-to-mouth existence, relying on funds from local governments to subsidize the cost of care for the medically indigent. Unfortunately, these same cities are also besieged by the current drug epidemic so that these institutions must deal not only with the increased burden of AIDS, but also with the morbidity and mortality associated with crack/cocaine.

While their public health institutions are struggling to cope with these serious problems, these municipalities, particularly those in the Northeast, also face serious economic problems. Despite the increased needs associated with AIDS and the drug epidemic in these cities, medical and social care systems for the poor must cope with fixed or declining resources. This serious lack of resources imperils the care not only for children with AIDS, but for all who must rely on these systems for medical care.

EFFECT ON THE FAMILY

Any serious, chronic disease obviously affects the function of the entire family, including adults and siblings, as well as the ill child. But AIDS is even more catastrophic for families. Because most children have been infected by their mothers during pregnancy, the family must deal not only with the disease in the child, but also in the mother and often in the father. While the problems of children with AIDS have been widely publicized in the lay press, the fact that virtually all their mothers are infected and thus at risk for developing the disease has not been equally appreciated. However, estimates from the New York City Department of Health suggest that in that city alone, some 40 000 children may be orphaned by AIDS during the next decade (Pauline Thomas, MD, director of AIDS and HIV Surveillance, oral communication, September 1990). Finally, despite considerable efforts at public and professional education, the fear of AIDS with the resulting discrimination makes the care and support of these unfortunate children and their families even more problematic.

A CALL TO ACTION

The story of AIDS in children mirrors our lack of concern for the poor children of this nation. In our current national obsession with budget deficits, the needs of constituencies with political power, and foreign policy issues, the care and welfare of the nation's children do not seem to have a high priority in the national agenda. While our political rhetoric may deny such an assertion, actions speak louder than words. The reality is that we are unwilling to provide the resources necessary to provide medical care to children with AIDS, to provide medical care to all poor children, or even to provide them with adequate housing or education.

To solve the problems of children with AIDS and indeed of all poor children, we must develop a simple method of financing medical care for the poor. For large numbers of families and children to have no access to medical care because of a lack of financial resources is simply unacceptable. Over the years, any number of proposals to remove the financial barriers to health care have been debated. A detailed analysis of these proposals is beyond the scope of this essay, but one thing is clear: any remedy to this problem must have much simpler administrative procedures than does our current highly bureaucratic Medicaid system. While money is a necessity, it is not sufficient for the humane care of these children and their families who represent some of the most socially isolated and bereft of our society. We must develop social support, housing, and respite systems that afford them the compassion and care that any of us would need in the face of such a devastating illness.

A nation that neglects its children places itself in greater danger than any foreign power could possibly muster. The clich´e is true: children are the future of the country. If we do not begin to attend to the needs of children with AIDS, indeed all children in poverty, the final judgment of history will surely be very harsh indeed.

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Pediatric Human Immunodeficiency Virus Infection and the Acquired Immunodeficiency Syndrome

A Health Care Crisis of Children and Families

Russell B. Van Dyke, MD

The number of children infected with the human immu-deficiency virus (HIV) is rapidly increasing. Most infected ildren acquire their infection by vertical transmission om an infected mother, and this increase in the number of ected children reflects a similar increase in the number infected women. Many features of HIV infection in chil-en differ from those in adults, and it is important for the iysician to be familiar with the varied presentations of pe-atric HIV infection. Transmission of HIV during adoles-nce, by sexual contact and illicit drug use, is also a growing oblem, accounting for most cases of acquired immuno-ficiency syndrome (AIDS) seen in young adults in their 's. The HIV-infected child represents only one member of amily affected by the HIV virus; frequently, multiple other embers of the family are infected as well. These families e predominantly underprivileged, coming from inner city inority populations with limited access to medical care and cial service support. Pediatric AIDS is a preventable dis-ise, by the prevention of HIV infection in women. In short rm, it is likely that education will have the greatest impact altering the course of the AIDS epidemic. Most infected iildren are cared for in a limited number of public inner ty hospitals, and the ability of these hospitals to continue provide adequate care will be threatened by the rising imber of cases. A multidisciplinary approach to providing ire for these children and their families is essential, with e primary care physician coordinating this effort. Rapid lvances in the treatment of HIV and its associated oppor-inistic diseases raise difficult questions concerning the ac-ess of women, including pregnant women, and children to linical trials of investigational agents. The commitment of idividual health care workers and an increased level of fi-ancial support will be necessary to provide the care that iese children and their families require and deserve.

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The acquired immunodeficiency syndrome (AIDS) was first recognized in the United States in 1981 as a disease ccurring in homosexual men. However, as the epidemic volved, the disease appeared in other groups, including hemophiliacs, intravenous drug users, women, and children. Currently, children less than 13 years of age comprise 1.8% of all cases of AIDS in the United States; by the end of 1991, it is estimated that there will be approximately 3000 pediatric AIDS cases in the United States. Most cases of AIDS in children result from the vertical transmission of human immunodeficiency virus (HIV) from an infected mother to her child, and the rising number of pediatric AIDS cases reflects a parallel rise in the number of HIV-infected women. Between 20% and 40% of infants born to an HIV-infected mother become infected themselves.[1-3] Factors that influence the transmission rate are not clearly defined, but maternal antibodies directed against specific portions of HIV surface glycoproteins appear to be an important factor in protecting the infant from infection.[4-6]

The proportion of AIDS cases in the United States that occur in women has been rising steadily since the onset of the epidemic and currently stands at 11% of all reported cases. Between 1988 and 1989, the number of cases in women increased by 29%, while the number in men rose by only 18%.[7] Approximately one half of women with AIDS acquired their infection through parenteral drug use, while one third acquired their infection through heterosexual transmission. Most HIV-infected women are of childbearing age. The proportion of AIDS cases in the United States due to heterosexual transmission increased from 0.9% in 1983 to 6% in 1990, with this rise expected to continue. This emphasizes that HIV is fundamentally a sexually transmitted disease, spread by both heterosexual and homosexual contact. Heterosexual transmission is the principal route of transmission of HIV in many developing countries and is playing an increasingly important role in the United States.

Although many of the clinical features of HIV infection are similar in adults and children, some are unique to children.[3] The typical clinical presentation of pediatric AIDS includes growth failure, developmental delay, hepatosplenomegaly, diffuse lymphadenopathy, recurrent bacterial infections, and chronic *Candida* infections. However, in many children the infection presents in an atypical fashion, manifesting isolated features of the disease, such as thrombocytopenia, pneumonia, parotitis, diarrhea, recurrent infections, failure to thrive, or loss of developmental milestones. Involvement of the central nervous system is a particularly important problem in children with HIV

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infection. Since children have not yet reached physical and developmental maturity, early features of HIV infection include poor growth and loss of mental and motor milestones. The immunologic immaturity and naïveté of children makes them prone to recurrent infections with common bacterial pathogens.

Infection with HIV must now be considered when a broad range of common and uncommon clinical syndromes are seen in children. Testing for HIV should be performed as part of the diagnostic evaluation of these children, whether or not risk factors for HIV infection are present. Consequently, the clinician must understand the difficulties in establishing HIV infection in children, particularly in those less than 15 months of age, in whom maternal antibody can result in a falsely positive HIV antibody test.[9] The results of HIV testing must be kept confidential. I believe that parents should be informed whenever HIV testing is performed on their child, but informed consent is usually not required unless mandated locally. Concerns about confidentiality should not prevent a child from being examined for HIV infection when appropriate.

Infection with HIV in the adolescent is a problem that deserves special attention. Currently, only 3.8% of AIDS cases in the United States occur in individuals between 13 and 19 years of age. However, the proportion of cases in this age group due to heterosexual transmission has increased substantially in recent years and currently stands at 23% for male patients and 44% for female patients.[10] Females currently make up 20% of adolescents with AIDS, in contrast to only 9% of adults with AIDS, further pointing out that heterosexual transmission plays a major role in the spread of HIV during adolescence.

Furthermore, these figures underestimate the importance of HIV *transmission* during adolescence. Currently, 20% of all cases of AIDS occur in young adults between 20 and 29 years of age. Since the median incubation period of AIDS in adults is between 8 and 10 years, the majority of individuals who develop AIDS in their 20's acquired their HIV infection during adolescence. The growing problem of HIV transmission during adolescence requires a response directed toward prevention of infection. This is particularly important in light of the increasing proportion of adolescents who are sexually active. At the present time in the United States, 32% of 16-year-old girls and 70% of 18-year-old women engage in premarital sexual activity.[11] There are several reasons why adolescents are at increased risk of HIV infection: they have a greater risk of other sexually transmitted diseases than older persons, they are less likely to use barrier methods of contraception, and they frequently have multiple sexual partners.[12] However, adolescents are receptive to being taught about AIDS; Steiner et al[13] demonstrated an excellent level of knowledge about this disease among a group of adolescents in Wisconsin. One hopes that these young adults will apply this knowledge to their own behavior.

Pediatric AIDS is not only a disease of the child; it is a disease of the whole family unit. Eighty percent of children with AIDS, and nearly all seropositive infants, have a mother who is HIV infected. Frequently, the mother's sexual partner is infected, and other children in the family may be infected as well. A disproportionate number of children with AIDS belong to minority groups; 53% are black and 23% Hispanic. Most cases occur in inner-city populations, which suffer from poverty, racism, illicit drug use, inadequate housing, poor access to medical care, and a nonintact family unit. As the HIV infection progresses in the child's parents, they are unable to care adequately for themselves and their child, and it falls on the extended family or the community to provide this care. These children are very difficult to place in foster care and hospice care. Not surprisingly, then, the hospital often provides this care, resulting in a large number of hospitalized "boarder babies" in regions with a large number of pediatric AIDS cases. At Harlem Hospital (New York, NY), more than 20% of hospitalizations of children with AIDS resulted from social problems rather than medical needs. The mean length of stay for these boarder babies was 339 days, as opposed to 89 days for children cared for at home.[14] The cost of this care is great; in that report from 1988, the authors estimated the mean lifetime hospital cost for a child with AIDS to be greater than $90 000. The increased use of outpatient services and foster care substantially reduces unnecessary hospitalizations among these children.[15]

Pediatric AIDS has its greatest impact on those minority groups that have the poorest access to medical care and are least likely to benefit from advances being made in the prevention and treatment of this disease. Indeed, more than any other disease, pediatric AIDS highlights the deficiencies in the health care system that exists in the United States today. Our efforts at delivering health care to these disadvantaged children have not been completely successful. For example, less than two thirds of nonwhite children in the United States are up to date in their immunizations at 2 years of age.[16] It can only be hoped that we will be more successful at delivering preventive and therapeutic care to HIV-infected children.

The rising number of children with AIDS will impact all areas of health care and rapidly overwhelm those areas where cases are concentrated. Infection with HIV is currently the ninth leading cause of death among children aged 1 to 4 years in the United States. By the end of 1991, it is anticipated that children with AIDS will occupy 10% of all pediatric hospital beds in the United States.[17] Most of these children will not have private health insurance, and their medical care will be funded by such public sources as the Medicaid program. Of the children in our pediatric HIV clinic, approximately 90% qualify for Medicaid through the Aid to Families With Dependent Children program. An additional 5% qualify through participation in the Supplemental Security Income program, which is available only to those children who carry an AIDS diagnosis. The remaining 5% of children have other sources of insurance or do not qualify for Medicaid. Unfortunately, each state administers its own Medicaid program, and states have differing eligibility criteria and benefits. In many states, the level of reimbursement is too low to meet adequately the needs of the child. In addition, home nursing care, ambulatory care, foster care, hospice care, and social service support may not be available or have limited benefits in some states. Finally, many health care providers do not accept Medicaid patients, further limiting access of these children to medical care.

The impact of pediatric AIDS on the practice of pediatrics and the training of young pediatricians needs to be addressed. All pediatric subspecialists will need to develop expertise in the problems of HIV-infected children. However, in most instances, the pediatrician or family practitioner will provide primary care for these children. In the ideal situation, the primary care physician will work with a team of specialists, including pediatric subspecialists, nurses, social workers, nutritionists, and developmentalists. The assessment and treatment of HIV-infected children must become part of the curriculum of all pediatric and family practice training programs. It is hoped that the increasing number of HIV-infected children will not be seen as a deterrent to those entering the field of pediatrics, but rather as a challenge to those committed to the health of children and their families.

A major concern raised by those caring for HIV-infected children has been a delay in access to new forms of treatment. Children have traditionally been excluded from clinical trials involving new medications until efficacy has been demonstrated in adults. The intent of this is to protect the child from possible adverse effects of a new medication until efficacy is established and the profile of adverse reactions is known. Unfortunately, it also delays the initiation of clinical trials in children and ultimately the availability of effective new forms of therapy. For instance, zidovudine was not available to children until clinical trials in adults were completed. The AIDS Clinical Trials Group, a collaborative group of AIDS researchers funded by the National Institutes of Health, has an active group of pediatric investigators responsible for designing and conducting clinical trials in HIV-infected children. This group has been very vocal in this concern, and children and women are currently benefiting from early involvement in the evaluation of promising new agents.

A question that arises in designing treatment protocols for children is whether results obtained in adult trials should be applied to children. An example is the recent demonstration that the early administration of corticosteroids increases survival in adults with *Pneumocystis carinii* pneumonia.[18] There is reason to suspect that pediatric *P carinii* pneumonia may respond differently than adult disease, because it represents primary infection rather than reactivation disease. The pediatric members of the AIDS Clinical Trials Group are currently considering whether a similar trial should be conducted in children.

What should the response of the medical community be to the growing problem of HIV-infected children? In the short term, the most successful response to the AIDS epidemic will be in the area of prevention. Pediatric AIDS *is* a preventable disease—by the prevention of HIV infection in women of childbearing age. To protect themselves, all young adults must understand, before they become sexually active, that HIV is a sexually transmitted disease. They need access to counseling about HIV and other sexually transmitted diseases, and they need to know how to protect themselves from infection, including the use of condoms. In addition, they need to understand the risk of parenteral drug use. Information about HIV transmission and AIDS must be taught to all children while they are in middle or junior high school. Finally, women need greater access to HIV testing so that pregnancy prevention and termination can be considered by those who are infected. Guidelines for HIV testing of pregnant women have been published.[17]

The development of new forms of treatment for HIV and the opportunistic diseases associated with AIDS must be of the highest priority. It is gratifying that the AIDS Clinical Trials Group has recently identified pediatrics as a major area of emphasis, and funds have been made available for additional sites to conduct pediatric studies. Both clinical research and basic research in the field of AIDS deserve additional support.

It is currently unknown whether HIV infection can be prevented in the child born to an infected mother. We are hindered by a lack of understanding of two key points: when during gestation and delivery the child becomes infected, and why only one of three infants born to an infected mother becomes infected. The AIDS Clinical Trials Group is initiating a study to determine whether the administration of zidovudine during the second and third trimesters of pregnancy, and continued in the infant for 6 weeks after delivery, will interrupt perinatal transmission. Other strategies for the prevention of perinatal transmission being considered include passive and active immunization of the woman before delivery and the prevention of infection in the child after delivery by the administration of such agents as recombinant CD4, which blocks infection from being established. We clearly need to learn much more about the mechanism and immunology of perinatal HIV infection.

Because of the complex medical and social needs of HIV-infected children and their families, a multidisciplinary team approach to providing care is necessary. In our Pediatric HIV Clinic at Charity Hospital of New Orleans (La), primary ongoing care is provided by general pediatricians with an interest in HIV disease, supported by pediatric subspecialists in infectious diseases, hematology, neurology, and other subspecialties. Adolescents infected with HIV are cared for by an adolescent medicine physician in the pediatrics clinic. We are currently developing a combined mother-child clinic to allow HIV-infected mothers and their infants to be seen at the same clinic visit. This takes advantage of our observation that HIV-infected women are much more compliant with their child's care than with their own care. A case manager/social worker is assigned to each family to assist with financial arrangements, transportation to and from the clinic, home health care, and referrals to other health care agencies. Finally, a pediatric therapist and clinical psychologist assist in neurodevelopmental evaluations and provide physical therapy.

This multidisciplinary approach to providing care is expensive and requires the commitment of a large group of health care professionals. Funds must be made available to support these programs, and personnel must be trained to provide the care. Developed countries, such as the United States, have the resources to deliver this care; it remains to be seen whether we have the wisdom to insist that it be done.

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In Other AMA Journals

ARCHIVES OF OTOLARYNGOLOGY—HEAD & NECK SURGERY

Pediatric Sinusitis: The Role of Endoscopic Sinus Surgery in Cystic Fibrosis and Other Forms of Sinonasal Disease

J. Kevin Duplechain, MD;
John A. White, MD;
Robert H. Miller, MD
(*Arch Otolaryngol Head Neck Surg.* 1991;117:422-426)

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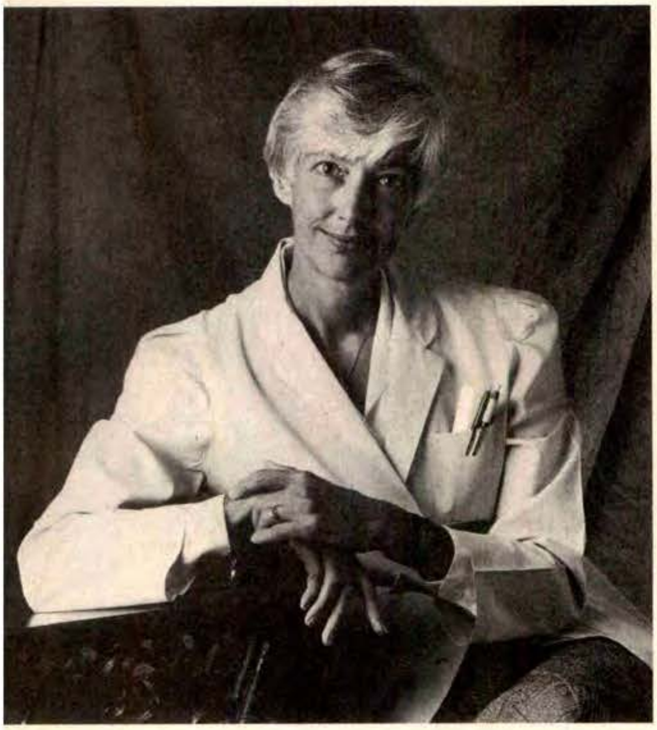

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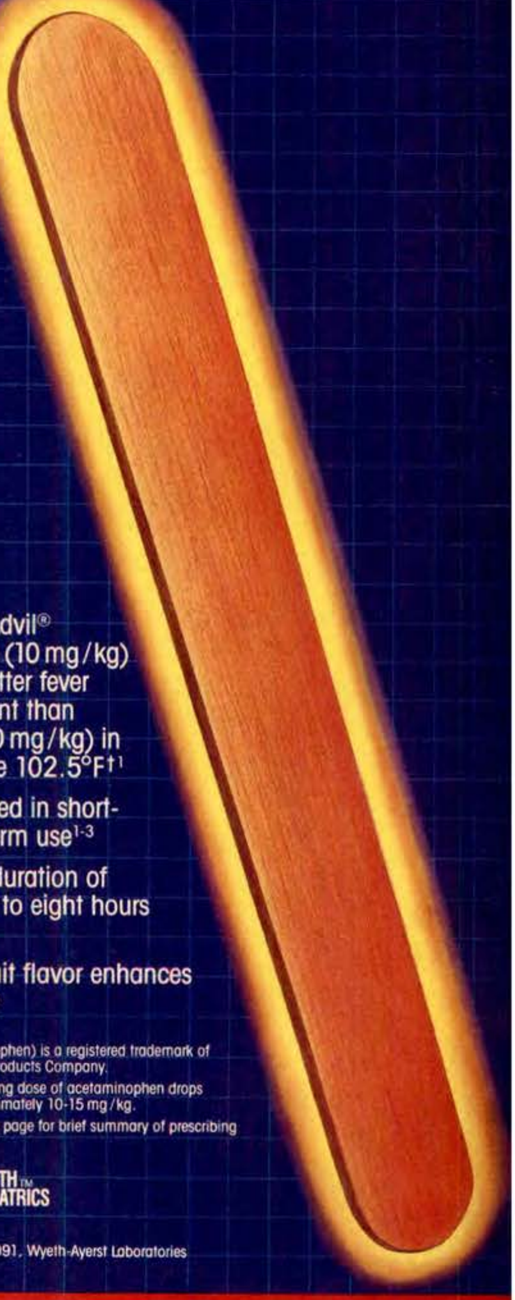

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INDICATIONS: CHILDREN'S ADVIL® SUSPENSION is indicated for the reduction of fever in patients aged 12 months and older, and for the relief of mild-to-moderate pain in patients aged 12 years and older.

CHILDREN'S ADVIL® SUSPENSION is also indicated for relief of the signs and symptoms of juvenile arthritis, rheumatoid arthritis, and osteoarthritis.

CHILDREN'S ADVIL® SUSPENSION is indicated for the relief of primary dysmenorrhea.

CONTRAINDICATIONS: Patients hypersensitive to ibuprofen or patients with all or part of the syndrome of nasal polyps, angioedema, and bronchospastic reactivity to aspirin or other nonsteroidal anti-inflammatory agents. Anaphylactoid reactions to ibuprofen have occurred in such patients.

WARNINGS: Risk of GI Ulcerations, Bleeding, and Perforation with NSAID Therapy: Physicians should remain alert for ulceration and bleeding in patients treated chronically with NSAIDS even in the absence of previous GI tract symptoms. In patients observed in clinical trials of several months' to two years' duration, symptomatic upper GI ulcers, gross bleeding or perforation appear to occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for one year.

Except for a prior history of serious GI events and other risk factors known to be associated with peptic ulcer disease, no risk factors have been associated with increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less well than other individuals and most spontaneous reports of fatal GI events are in this population.

PRECAUTIONS: General: Because serious GI tract ulceration and bleeding can occur without warning symptoms, physicians should follow chronically treated patients for the signs and symptoms of ulceration and bleeding.

Blurred and/or diminished vision, scotomata, and/or changes in color vision have been reported. If a patient develops such complaints the drug should be discontinued and the patient should have an ophthalmologic examination.

Fluid retention and edema have been reported with ibuprofen; therefore, the drug should be used with caution in patients with a history of cardiac decompensation or hypertension.

Ibuprofen can inhibit platelet aggregation and prolong bleeding time. CHILDREN'S ADVIL® SUSPENSION should be used with caution in persons with intrinsic coagulation defects and those on anticoagulant therapy.

The antipyretic and anti-inflammatory activity of ibuprofen may reduce fever and inflammation, thus diminishing their utility as diagnostic signs in detecting complications of presumed noninfectious, noninflammatory painful conditions.

Small decreases (usually not exceeding one gram) in hemoglobin and hematocrit with an apparent dose response relationship have been observed following chronic administration. If there are no signs of bleeding, it is probably not clinically important.

To avoid exacerbation of disease or adrenal insufficiency, patients on prolonged corticosteroid therapy should have their therapy tapered slowly when CHILDREN'S ADVIL® SUSPENSION is added to the treatment program.

Aseptic meningitis: Aseptic meningitis with fever and coma has been observed on rare occasions in adult patients on ibuprofen therapy. Although it is more likely to occur in patients with systemic lupus erythematosus and related connective tissue diseases, it has been reported in adult patients who do not have underlying chronic disease. If signs or symptoms of meningitis develop in a patient on CHILDREN'S ADVIL® SUSPENSION, the possibility of its being related to ibuprofen should be considered.

Renal Effects: As with other nonsteroidal anti-inflammatory drugs, long-term administration of ibuprofen to animals has resulted in renal papillary necrosis and other abnormal renal pathology. In humans, there have been reports of acute interstitial nephritis with hematuria, proteinuria, and occasionally nephrotic syndrome.

A second form of renal toxicity has been seen in patients with prerenal conditions leading to reduction in renal blood flow or blood volume. In these patients, administration of a nonsteroidal anti-inflammatory drug may cause a dose dependent reduction in prostaglandin formation and precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, and those taking diuretics and the elderly. Those patients at high risk who chronically take CHILDREN'S ADVIL® SUSPENSION should have renal function monitored if they have signs or symptoms of azotemia. Discontinuation of nonsteroidal anti-inflammatory drug therapy is typically followed by recovery to the pretreatment state.

Since ibuprofen is eliminated primarily by the kidneys, patients with significantly impaired renal function should be closely monitored and a reduction in dosage should be anticipated to avoid drug accumulation.

Information for Patients: Physicians may wish to discuss with their patients the potential risks and likely benefits of treatment with CHILDREN'S ADVIL® SUSPENSION.

Laboratory Tests: Meaningful (3 times the upper limit of normal) elevations of SGPT or SGOT (AST) occurred in controlled clinical trials in less than 1% of patients. A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of more severe hepatic reactions while on therapy with ibuprofen. If abnormal liver tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur, CHILDREN'S ADVIL® SUSPENSION should be discontinued.

Diabetes: Each 5 mL of CHILDREN'S ADVIL® SUSPENSION contains 2.5 g of sucrose which should be taken into consideration when treating patients with impaired glucose tolerance. It also contains 350 mg of sorbitol per 5 mL. Although in clinical trials CHILDREN'S ADVIL® SUSPENSION was not associated with more diarrhea than control treatments, should a patient develop diarrhea, the physician may wish to review the patient's dietary intake of sorbitol from other sources.

Drug Interactions: *Coumarin-type Anticoagulants:* Bleeding has been reported when ibuprofen and other nonsteroidal anti-inflammatory agents have been administered to patients on coumarin-type anticoagulants; the physician should be cautious when administering CHILDREN'S ADVIL® SUSPENSION to patients on anticoagulants.

Aspirin: Concurrent use of aspirin is not recommended.

Methotrexate: In vitro studies indicate that ibuprofen could enhance the toxicity of methotrexate. Caution should be used if CHILDREN'S ADVIL® SUSPENSION is administered concomitantly with methotrexate.

H_2 Antagonists: In studies with human volunteers, coadministration of cimetidine or ranitidine with ibuprofen had no substantive effect on ibuprofen serum concentrations.

Furosemide: Ibuprofen can reduce the natriuretic effect of furosemide and thiazides in some patients. During concomitant therapy with CHILDREN'S ADVIL® SUSPENSION, the patient should be observed closely for signs of renal failure as well as to assure diuretic efficacy.

Lithium: Ibuprofen produced an elevation of plasma lithium levels (15%) and a reduction in renal lithium clearance (19%) in a study of 11 normal volunteers during the period of concomitant drug administration. Patients should be observed carefully for signs of lithium toxicity. Read package insert for lithium before its use.

Pregnancy: Administration of ibuprofen is not recommended during pregnancy or for use by nursing mothers.

Infants: Safety and efficacy of CHILDREN'S ADVIL® SUSPENSION in children below the age of 12 months have not been established.

ADVERSE REACTIONS: The most frequent type of adverse reaction occurring with CHILDREN'S ADVIL® SUSPENSION is gastrointestinal. In clinical trials among adults involving chronic administration of ibuprofen, the percentage of patients reporting one or more gastrointestinal complaints ranged from 4% to 16%.

Incidence Greater Than 1% (but less than 3%), Probable Causal Relationship (see PRECAUTIONS): Abdominal cramps or pain, abdominal distress, constipation, diarrhea, epigastric pain,* fullness of the GI tract (bloating and flatulence), heartburn,* indigestion, nausea,* nausea and vomiting; dizziness,* headache, nervousness; pruritus, rash* (including maculopapular type); tinnitus; decreased appetite; edema, fluid retention (generally responds promptly to drug discontinuation).

Precise Incidence Unknown (but less than 1%), Probable Causal Relationship (see PRECAUTIONS): Abnormal liver function tests, gastric or duodenal ulcer with bleeding and/or perforation, gastritis, gastrointestinal hemorrhage, hepatitis, jaundice, melena, pancreatitis; alopecia, erythema multiforme, Stevens-Johnson syndrome, urticaria, vesiculobullous eruptions; aseptic meningitis with fever and coma, confusion, depression, emotional lability, insomnia, somnolence; amblyopia (blurred and/or diminished vision, scotomata and/or changes in color vision), hearing loss; agranulocytosis, aplastic anemia, decreases in hemoglobin and hematocrit, eosinophilia, hemolytic anemia (sometimes Coombs' positive), neutropenia, thrombocytopenia with or without purpura; congestive heart failure in patients with marginal cardiac function, elevated blood pressure, palpitations; anaphylaxis, bronchospasm (see CONTRAINDICATIONS), syndrome of abdominal pain, fever, chills, nausea and vomiting; acute renal failure in patients with pre-existing significantly impaired renal function, azotemia, cystitis, decreased creatinine clearance, hematuria, polyuria; dry eyes and mouth, gingival ulcers, rhinitis.

Precise Incidence Unknown (but less than 1%), Causal Relationship Unknown: Dream abnormalities, hallucinations, paresthesias, pseudotumor cerebri; photoallergic skin reactions, toxic epidermal necrolysis; cataracts, conjunctivitis, diplopia, optic neuritis; bleeding episodes (e.g., epistaxis, menorrhagia); acidosis, gynecomastia, hypoglycemic reactions; arrhythmias (sinus tachycardia, sinus bradycardia); angioedema, Henoch-Schönlein vasculitis, lupus erythematosus syndrome, serum sickness; renal papillary necrosis.

*Reactions occurring in 3% to 9% of adult patients treated with ibuprofen.

OVERDOSAGE: Patients with a history of ingestion of greater than 100 mg/kg should have induced emesis or gastric lavage. Multiple dose oral administration of activated charcoal may be useful. Supportive therapy may include oxygen, respiratory support, and parenteral fluids. Because the drug is acidic and excreted in the urine, administration of sodium bicarbonate and induction of diuresis may be beneficial.

DOSAGE AND ADMINISTRATION: Fever: 5 mg/kg if baseline temperature is 102.5°F or below or 10 mg/kg if baseline temperature is greater than 102.5°F, every 6-8 hours (children); 400 mg every 4-6 hours (adults).

Mild to moderate pain in adults: 400 mg every 4 to 6 hours.
Juvenile Arthritis: 30-40 mg/kg day in 3 or 4 divided doses.
RA and OA: 1200-3200 mg per day in 3 or 4 divided doses.
Dysmenorrhea: 400 mg every 4 hours.

HOW SUPPLIED: 4 and 16 oz. bottles

Caution: Federal law prohibits dispensing without prescription.

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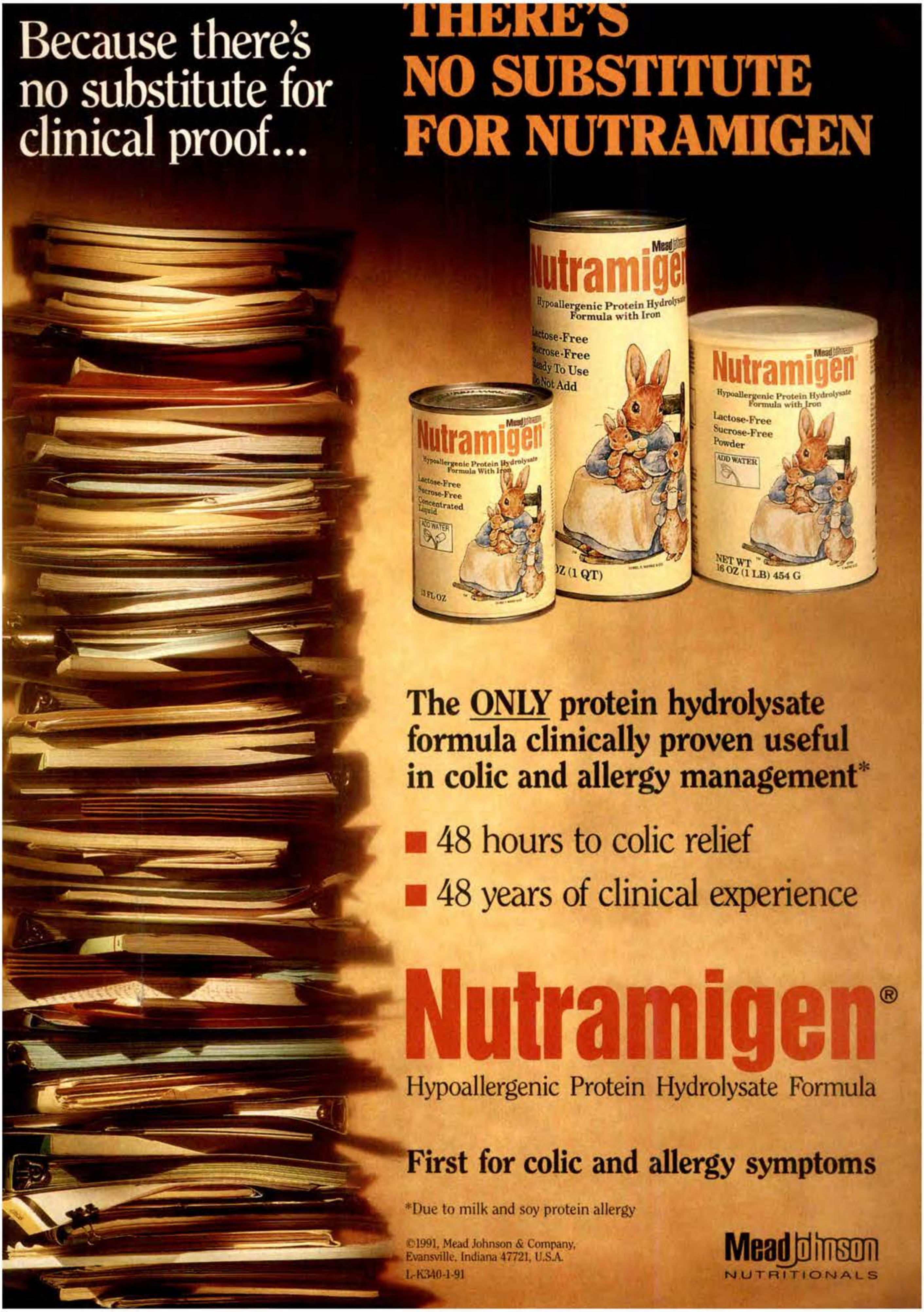

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NUTRITIONALS

The American Academy of Pediatrics Response to the Growing Health Needs of Children

James E. Strain, MD

At its planning meeting in May 1988, the executive board of the American Academy of Pediatrics (AAP) established the promotion of access to child health care as its top priority. Later in the year, the following resolution was passed at the chapter president's forum: "That the Academy develop and support legislation to assure a health program that guarantees all children and pregnant women access to a comprehensive (basic) package of health care benefits that treats all children and pregnant women equally, and that the Academy work with legislators to draft a model program that, to the extent practicable, maintains parental control of health care decisions, preserves the physician's primary obligation to his or her patient, and effectively utilizes private insurers."

In October 1988, the executive board approved a universal access-to-care proposal consisting of three components: (1) the introduction of federal legislation that guarantees financial access to medical care for all children and pregnant women; (2) the establishment of community-based health projects that meet the special needs of children at the local level; and (3) the introduction of a public relations program that increases public awareness of the importance of child health issues. The three components of the AAP access initiative are described in this article.

FEDERAL LEGISLATION

In 1987, approximately 10 million children aged 0 through 21 years were without health insurance for the entire year. Another 10 million were uninsured for part of the year.[1] Employers faced with escalating insurance costs are increasing employees' share of premium costs for dependents, thereby discouraging dependent coverage.[2] In addition, plans that do cover dependents often fail to meet the health needs of children. Most child health services are provided in an ambulatory setting and are often not covered by health insurance. Traditional insurance has been designed to cover hospital care. While this type of coverage is important for the occasional child with a catastrophic or long-term illness, the vast majority of children will have no need for this service.

Some children are classified as uninsurable because of a preexisting condition. Children with congenital defects, chronic diseases, or other disabling conditions are often excluded from coverage, particularly when a parent changes jobs. Insurance companies are reluctant to accept children who may require more than the usual amount of care.

More than one in five children in this nation live in poverty. About half of the poor children are receiving Medicaid benefits. Although 52% of those eligible for Medicaid are children, less than 20% of Medicaid dollars are spent for their care.[4] Thus, in both the private and public sectors, there are significant gaps in the health insurance coverage for children.

Uninsured children utilize physician services less often than do insured children,[5,6] particularly preventive health services.[6] Delays in treatment often add to the cost of care and reduce the likelihood of a successful outcome.

To meet the needs of all children, including the uninsured, underinsured, and uninsurable, the AAP has developed a proposal that guarantees financial access to care for all children through age 21 years and all pregnant women. This plan is designed to be the least disruptive of the present health care system. It is a one-tiered system in which children insured in the private and public sectors have equal benefits. These benefits include preventive health services, the treatment of acute and chronic illnesses, and the management of disabling conditions that require care coordination. Standards of care will be set at the federal level, but administration of the program will be left to the states. The cost of the program will be borne by the public and private sectors, and families that can afford to pay will share in the costs. There will be a fair and equitable payment for services rendered and a simplified billing system.

THE AAP PLAN

Benefits

Benefits include preventive health care, primary medical care, and extended care requiring coordination of services.

1. Preventive health care includes the following: (*a*) office visits, immunizations, and laboratory services as recommended by the AAP in its periodicity schedule; (*b*) maternity services; (*c*) family planning services; (*d*) care of the newborn, including physician attendance at high-risk deliveries; (*e*) child abuse and neglect assessment; and (*f*) preventive dental care. Because of the importance of preventive health care, there will be no copayments or deductibles for anyone receiving these services.
2. Primary medical care includes the following: (*a*) hospital care; (*b*) physician services for acute and chronic conditions; (*c*) laboratory and other diagnostic services; (*d*) acute dental care; (*e*) medical and surgical supplies; (*f*) corrective eyeglasses and lenses; (*g*) hearing aids; (*h*) medical equipment; and (*i*) prescription drugs, including nutritional supplements. For families below 133% of the poverty level, no coinsurance or deductibles will be required for these services. For those above 200% of the poverty level, there will be a $200 annual deductible per family and a 20% copayment. A sliding scale will be used for families between 133% and 200% of the poverty level.
3. Extended medical care requiring care coordination includes the following: (*a*) care coordination for chronically ill and other "at risk" children; (*b*) orthodontia; (*c*) treatment of developmental and learning disabilities; (*d*) substance abuse services; (*e*) speech

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From the American Academy of Pediatrics, Elk Grove Village, Ill.
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therapy; (*f*) occupational therapy; (*g*) physical therapy; (*h*) hospice care; (*i*) respite care; (*j*) recuperative stays in long-term care facilities; and (*k*) nutritional assessment and counseling. For those above 200% of the poverty level, there will be a maximum coinsurance of 30% for these services. No copayments or deductibles will be required of families with incomes below 133% of poverty. A sliding scale will be used for families between 133% and 200% of poverty. There will be an out-of-pocket cap of 10% of family income or $1000 per year for an individual and $3000 per family, whichever is less, for all services provided under the plan.

To the extent possible, insurance mechanisms will be used to fund benefits included in the AAP proposal. However, direct state or federal funding will be required for some services. Services for children with special health care needs and primary care services where none are locally available are among those that may need direct funding. The state Title V maternal and child health agencies will continue to play an important role in monitoring care and providing services not covered by insurance.

Financing

Funding for this plan will come from private and public sources. In the private sector, employers will be required to provide the mandated benefit package for children and pregnant women or pay a 3.17% employee payroll tax based on 1990 calculations. The shared cost of dependent coverage cannot be a greater percentage of the total premium than the shared cost of the employee coverage and cannot exceed 25% of the total premium.

In the public sector, a fund will be established at the state level to purchase insurance for families not covered by employer insurance. It will have several income streams. The tax imposed on employers who elect not to provide coverage for dependents of their employees or whose benefit package fails to meet mandated benefit standards will be one source of funding. Federal and state Medicaid funds currently being used to provide medical services for children and pregnant women will be another source. Finally, premiums paid by families not covered by employer insurance will be added to the fund. If the family income is above 200% of the poverty level, an annual premium of $458 will be paid per family. No premium payments will be required for those families below 133% of the poverty level, and a sliding scale will be used to determine the premium costs for families falling between 133% and 200% of the poverty level.

Multiple private insurers will bid on the state contracts just as they do in the private sector. The benefit package must be the same for employer insurance and for the state-administered fund. In the required package, insurers will be allowed some flexibility in the scope and duration of benefits and in the amount of cost sharing, provided the plan is actuarially equivalent.

Administration

The federal government will mandate a benefit package. The Secretary of the US Department of Health and Human Services will have the authority to establish boundaries within which the states must function.

The actual administration of the program will be at the state level. States will establish policies that control marketing of insurance and will develop and maintain the system. They will monitor the health status of children and pregnant women and will collect data on unmet needs. They will be responsible for regulating fiscal intermediaries and for developing performance standards for insurers.

COMMENT

The AAP plan replaces the children's and pregnant women's portions of Medicaid. Medicaid has perpetuated a two-tiered system of care in which eligibility, benefits, and reimbursement limited by lack of funds, vary from state to state. Physician participation in Medicaid has declined in recent years.[6] Billing procedures have become burdensome.

The plan proposed by the AAP provides a uniform package of benefits for all children and pregnant women. It is an insurance-based program with private insurers bidding for contracts in the public and private sectors. It provides for cost sharing of premiums, copayments, and deductibles based on the ability to pay. It underwrites the cost of care for the poor.

The AAP's proposal will increase the total cost of health services for children and pregnant women from the 1990 level of $98.8 billion to $111.4 billion, an increase of approximately $12 billion. Compared with the total cost of medical care in the United States, which was $650 billion in 1990,[7] the added cost of providing health care for all children and pregnant women is relatively low.

The AAP intends to introduce legislation in the 1991 session of Congress that incorporates the principles enunciated in the plan. Because of the widespread dissatisfaction with the current methods of financing health care, it is likely that many new health care financing proposals will be considered by the 102nd Congress. The AAP plan is the only one that specifically addresses the care of children and pregnant women. The AAP supports guaranteed financial access to care for all United States citizens, but we believe that if an incremental approach is necessary, the first step should be coverage for children and pregnant women. The value of preventive care and early intervention for children and pregnant women, the relatively low cost, and the large number of women and children living in poverty are strong arguments for making children and pregnant women our top priority.

Community-Based Programs

While providing health insurance for all children and pregnant women is an important first step in guaranteeing access to medical care, it is clearly not the total solution to the mounting health problems of the young. Poverty and its social consequences account for much of the morbidity in our nation's children. Until mothers and children live in a safe environment and have sufficient food and adequate housing, the availability of medical care will have limited impact on the health of our children.

These societal problems are beyond the scope of activity of the AAP; however, we should be able to address many nonfinancial barriers to health care. For example, there are inadequate numbers of health professionals to deliver care in some parts of the country, particularly in rural and inner-city areas. Transportation to and from the sources of care can be difficult when medical care is not readily accessible. The process of enrollment in the Medicaid program is often difficult and demeaning. Many of the Medicaid registration requirements appear to be designed to keep children out of the program rather than bring them in.

In addition, cultural differences sometimes make it difficult for families to use traditional health care services. They often feel ill-at-ease in physicians' offices or in emergency centers. Reliance on folklore medicine is common among some ethnic groups.

The AAP believes that many of these problems can be solved at the local level. Communities understand the health needs of their children and, given the necessary resources, are able to develop programs that meet those needs.

To assist communities in this effort, the AAP initiated two community-based programs. The first, "The Healthy Tomorrows Partnership For Children," is a program funded by the federal Maternal and Child Health Bureau and jointly administered with the AAP. The program is designed to fund community-based projects in areas where access to care is limited and child health needs are not being met. A funded program receives $50 000 each year for 5 years provided that annual matching funds of $100 000 are obtained from local sources. An additional requirement is the participation of the local pediatric community and the state Maternal and Child Health Agency.

In 1989, 113 grant applications were submitted. Ten were selected by a panel of experts appointed by the AAP and Maternal and Child Health Bureau. Among the projects selected were the Family Care Center Health Project in Lexington, Ky; the Healthy Start Children's Clinic in Fort Collins, Colo; the Parent-Pediatric Partnership in Honolulu, Hawaii; and Project Caring in Pittsburgh, Pa. Site visits were carried out by members of the AAP Project Advisory Committee and each of the 10 programs has been approved for continued funding for a second year.

The program was continued in 1990 with the selection of 10 additional projects, all created to meet the special needs of children in local communities. These include the Jackson County Prenatal Clinic in Jackson, Mich; the First Steps Primary Program in Baton Rouge, La; and the Rural Partnership For Children in Omaha, Neb.

The second AAP community-based effort is the Healthy Children program, originally conceived and directed by Philip Porter, MD, and funded by the Robert Wood Johnson Foundation. Dr Porter has had great success during the past 20 years in helping communities recognize their child health needs and sharing with them the experiences of other communities. He has accomplished this by providing consultants from other successful programs and advising on new and innovative ways to secure local funding. Among the programs developed with the assistance of Dr Porter are a school-based primary care program, a program for social enrichment and primary care of preschool children, a pregnancy prevention program, a comprehensive primary care program for mothers and children, and a program for the care of handicapped children in rural America.

Healthy Children has demonstrated that a broad base of community leadership is needed to successfully introduce a health care program at the community level. Public health officials, school administrators, political leaders, nurses, child advocates, church leaders, and pediatricians all bring special skills and experience to the programs. All can play a significant role in meeting the needs of children in their communities.

During the past 2 years, as a result of funding from the Robert Wood Johnson Foundation, the Healthy Children concepts have been incorporated into an AAP program to assist local communities in their planning efforts. The program does not make grants, but provides technical assistance and advice under the direction of Dr Porter. Forty thousand pediatricians have learned about the program through direct mailings from the AAP. Using the existing network of state AAP chapters, pediatricians with a special interest in community-based activities have been identified and have agreed to serve as state facilitators.

In August 1990, these facilitators met in Chicago, Ill, to discuss their programs and share information. This very successful conference laid the groundwork for future development of community-based programs throughout the country. In addition, lessons learned from these programs can contribute to a better understanding of child health needs and to the establishment of an effective national child health policy.

Public Awareness Program

The third component of the AAP access initiative is the public awareness program. The public must become convinced of the importance of child health to the future of the nation. We must assume responsibility for the health of all of our children—rich and poor, black and white, disabled and healthy. This will require a commitment on the part of the public and, ultimately, state and federal legislators to put children's issues first. The AAP expects to accomplish this with the public awareness program.

Health professionals have an important role to play in keeping children healthy and in treating their illnesses. However, other factors are equally important. A polluted environment can have serious health consequences. Lead and toxic chemicals can have damaging effects on children.[8,9] Certain activities related to life-styles, such as substance abuse and risk-taking behaviors, have an immediate impact on health. Inappropriate diets, sedentary behavior, and tobacco use can also have long-term consequences.

There is a definite relation between health and education. An unhealthy child will not do well in school. In 1988, there were 4 300 000 children and young adults aged 14 to 24 years who did not attend school regularly and/or had not completed 12th grade or received a general equivalency degree.[10] Many children who do graduate are functionally illiterate. These are alarming statistics in a nation that is being forced to compete in the world market. Children's health and education go hand in hand and must be our nation's highest priorities.

These messages will be taken to the public with the assistance of a national public relations firm. Marketing a product is difficult and expensive. Marketing an idea is even more challenging. The AAP intends to seek industry support for programs that highlight solutions to the problems of children. We believe industry is interested, not only from a humanistic point of view, but also out of concern for the health and education of our nation's future work force. Contributions from foundations and individuals will also be solicited to support the public awareness program.

The AAP also recognizes that there are other groups with an interest in promoting child health. We intend to work with these organizations to enhance their activities and to broaden their scope of influence.

The specific objectives of the public awareness program are (1) to convince business leaders, legislators, and the public at large of the importance of child health and the long-term benefits of improving the health of our nation's children, and (2) to generate public support for improving access to care for children and pregnant women by defining the barriers to care and the means of overcoming those barriers.

The AAP is under no illusion that changing public opinion or creating a ground swell of public support for children's health issues will be easily accomplished, but over a period of time, we believe an informed and aroused public will demand that children's issues be given a higher priority on the legislative agenda.

The AAP invites the support and participation of all pediatric organizations and other child advocates in these important child health initiatives.

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BOOK REVIEW

Seizures and Epilepsy in Childhood: A Guide for Parents

By John M. Freeman, Eileen P. G. Vining, and Diana J. Pillas, 287 pp, $18.95, Baltimore, Md, Johns Hopkins University Press, 1990.

Good books for parents of children with seizures are hard to come by. This new volume fills a much-needed gap. Written by two pediatric neurologists and a clinic coordinator–counselor from the Pediatric Epilepsy Center at The Johns Hopkins Medical Institutions (Baltimore, Md), the book addresses both the medical facts about seizure disorders and the fears and concerns of parents.

The book is divided into five parts: why seizures occur; diagnosing and treating seizures and epilepsy; treating seizures and epilepsy; coping with epilepsy; and living with epilepsy. Using clinical examples, tables, and illustrations, the areas are clearly and matter-of-factly reviewed. The "new" and "old" systems of classification of epilepsy are included, as well as simplified neuroanatomy and sample electroencephalograms. Because I agree strongly, I was delighted to see the authors state, "It is not necessary to do a CT or MRI scan on every child who has had a first seizure" (page 103). Discussion of therapy is simple but thorough, as are the chapters on school, driving, participation in sports, insurance, and support organizations such as the Epilepsy Foundation of America.

Toward the end of the book, the authors state, "There are no references in this book because the information about epilepsy is changing and evolving. Parents are encouraged to contact the Epilepsy Foundation of America for further information." This seems like a bit of a shortcut; other references could have been included for completeness. Finally, an excellent glossary is included at the end for parents bewildered by the terminology of epilepsy and seizures.

Peggy C. Ferry, MD
Section of Child Neurology
Department of Pediatrics
University of Arizona
College of Medicine
1501 N Campbell
Tucson, AZ 85724

The Growing Neglect of American Children

Harold M. Maurer, MD

America is not doing enough to meet the health care needs of poor children. Unless we face up to this growing neglect, our nation's future is in doubt. Although we frequently hear that "children are our greatest national resource," we see little evidence to indicate that our policy makers believe it or are willing to act to prevent the terrible waste in human resources as a result of poverty. The money spent on health care for the elderly in America is 15 times that spent on health care for children.[1] Although children represent 50% of the Medicaid population, they receive less than 20% of the money spent for health services.[1] Furthermore, Medicaid reimbursement for health services for children is so low that few physicians in private practice can afford to see Medicaid patients.

The facts regarding impoverished children are staggering. They are cause for concern regarding the values and priorities of our nation. The data speak for themselves.

1. Thirty-seven million American children live in poverty, 9 to 12 million have no health insurance, and millions of others have less than adequate health insurance.[2] Children are the poorest group in society.
2. One in four to six pregnant women lacks health insurance for maternity care, and one in four does not receive prenatal care during the first trimester.[2]
3. The infant mortality rate is higher in America than in some third-world countries. In 1989, there were 9.7 deaths per 1000 live births; it was twice that for blacks.[3]
4. Nearly 5000 low-birth-weight babies are born every week in America.[1] Low birth weight, which, in many instances, is preventable through improved prenatal care for the mother, places these babies at high risk for serious illness and handicapping condi-tions.[1]
5. Each year, as many as 1 million teenagers become pregnant, and 18% of newborn infants in some city hospitals are victims of transplacental exposure to alcohol, crack, and other hard drugs (*The New York Times Magazine*. September 9, 1990:41).
6. One third of poor children are not immunized by the second year of life against measles, mumps, and rubella.[2] Ten percent of children younger than 4 years have not seen a physician in a year.[2] Poor children tend to be taken episodically to costly city or county hospital emergency departments for care, often late in the course of an illness. Because poor children lack a "medical home," they often do not receive continuing care, anticipatory guidance, or counseling, which could eliminate preventable health problems.

America must come to grips with these devastating but correctable problems. We have the knowledge to prevent illness, promote health, and save lives. We must provide access to health and social services for all pregnant women and children through the provision of universal health insurance. The plan proposed by the American Academy of Pediatrics meets this objective, and this plan or an equivalent one should be enacted into law. In addition, we must provide a "medical home" for every pregnant woman and child so that primary health and continuity of care can be provided to promote health. Widening medical coverage alone to cover more pregnant women may not be the answer. Women must be able to enroll before they become pregnant, or else they may become pregnant months before they sign up. The application process also needs to be accelerated and health care should be provided during the processing of the application. We should support all programs, agencies, policies, and strategies that guarantee the full spectrum of health care services for these underserved.

Expanding access to health care will also affect health manpower needs. More primary care physicians will be required to care for the population of pregnant women and children who are currently underserved, or whose needs are not being met. Resident physician education should include a curriculum segment that deals with the specific health care needs of the poor.[4] Moreover, incentives such as loan forgiveness should be created to attract residents to pursue careers in serving the poor.

During the next century, we can expect considerable change in the demographics of our nation. The current migration of people throughout the world is greater than ever before. The distinction between minority and majority groups will fade. In the next century minority groups will become the majority of the population in the United States. It is essential that we recognize this changing environment and begin to provide access to health care for poor women who do not receive prenatal care and for poor children in our society. We must ensure that every child has the opportunity to grow up healthy, gain an education, and become economically productive.

The following are the members of the Executive Committee of the Association of Medical School Pediatric Department Chairmen Inc: Robert F. Kelch, MD, president; Ralph Feigin, MD, president-elect; Michael A. Simmons, MD, secretary-treasurer; George W. Brumley,

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From the Association of Medical School Pediatric Department Chairmen Inc, Salt Lake City, Utah, and the Department of Pediatrics, Children's Medical Center, Medical College of Virginia, Virginia Commonwealth University, Richmond.

Reprint requests to the Department of Pediatrics, Children's Medical Center, Medical College of Virginia, Virginia Commonwealth University, Richmond, VA 23298 (Dr Maurer).

MD; Robert A. Hoekelman, MD; Harold M. Maurer, MD; Donald N. Mederis, Jr, MD; Alfred E. Michael, MD; Carol F. Phillips, MD; Irving Schulman, MD; James A. Stockman III, MD.

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BOOK REVIEW

Difficult Diagnosis in Pediatrics

Edited by J. A. Stockman III, 464 pp, $45, Philadelphia, Pa, WB Saunders Co, 1990.

Books for the general physician who encounters children with difficult diagnoses and management problems are few, but in great demand. The major pediatric textbooks emphasize individual diseases rather than problems of diagnosis and management. This book attempts to fill that void.

The book is divided into two sections. We are told that the first section deals with approaches to evaluations of common problems and that the second section deals with specific disease entities that are difficult to diagnose or to distinguish from similar disorders. I was confused by exactly how each chapter was chosen for one section vs the other, and, therefore, this division into two sections did not help organize the book for me. Nevertheless, each chapter easily stands by itself. The book discusses a broad spectrum of disease categories, but as Stockman warns in his introduction, the list can hardly be comprehensive.

While reading each chapter, it seemed I was sitting at grand rounds listening to the author. Included in the discussion is the pathophysiology of the disease and a thorough differential diagnosis of the problem. The biochemical, radiologic, and other techniques available to evaluate each problem are then described. The chapters are stimulating and often information-packed.

The topics are usually presented with a subspecialty orientation. The bulk of each chapter is not devoted to the most likely diagnosis to be encountered by the generalist but instead focuses on the most difficult disorders for subspecialists to distinguish and diagnose. A good example of this is in the chapter on hyperbilirubinemia. Physiologic and breast milk jaundice are discussed only briefly. Most of the discussion centers on intrahepatic and extrahepatic causes of cholestatic jaundice. The choice of topics also reflects a subspecialty bias. Poor glucose control, chronic interstitial pneumonia, unexplained acidosis, and acute hepatic failure thankfully are only occasionally encountered by most generalists, but are more typical of problems faced by the subspecialist.

There are a few excellent chapters on problems that generalists encounter more frequently. Chapters entitled "Innocent Murmurs," the "Nonsleeping Child," and "Growing Pains" discuss the initial outpatient evaluation and suggest when a more in-depth evaluation will be needed and the optimal time at which the input of a subspecialist will be helpful. The chapter on failure to thrive is one of the best I have read. It minimizes the importance of laboratory screening tests and includes a well-developed discussion of the importance of psychosocial issues in the work-up. Those chapters turned out to be my favorites, but perhaps they give the book too broad an audience.

Busy practitioners will be disappointed if they purchase this book only for quick guidance to the evaluation of a variety of symptoms or problems. While controversies in management and therapeutics are discussed, the discussion focuses on subspecialty procedures. The view presented is that general pediatricians should continue to have input in determining if and when procedures such as skin biopsies, bronchoscopies, or D-xylose absorption tests should be performed, although they rarely perform and/or interpret these evaluations by themselves. This book is not meant to replace the subspecialist.

All general pediatricians undoubtedly will encounter many patients who defy diagnosis and and whose conditions require subspecialty consultation. To manage these patients, the general pediatrician must be able to work with other physicians and coordinate the care of patients with difficult problems. This is a difficult but vital job that requires a tremendous breadth of knowledge to perform well. Books like this are in demand by all physicians who seek to broaden their knowledge and understand the approaches used by specialists. The medical student and pediatric resident working at a referral center, who will see every day the problems discussed in this book, especially will find this book ideal.

ROBERT KAMEI, MD
San Francisco, Calif

The Challenge of Care for the Poor Child

The Research Agenda

Steve Kohl, MD

The Society for Pediatric Research is a diverse group of scientists bonded by the common interest in research dealing with problems of children. Many of the society's members have very strong feelings regarding the social and political problems of health care for the poor and, in particular, health care for poor children. Nevertheless, it is not in the usual scope of our organization to comment as a group on these problems or even to claim particular expertise in this area. Indeed, other segments of the pediatric community have been asked to address these issues, and their efforts can be found in this issue.

As a research-oriented organization, the Society for Pediatric Research can make cogent comments and suggestions concerning the role of investigation in this problem area. In this regard, one must view research in its broadest sense; that is, research on the molecular level at one end to research on the societal level at the other end. There is a clear and pressing role for research methods in identifying the problems facing the poor and in arriving at rational solutions to them on all levels.

To enumerate many of the health problems particularly facing poor children in this country would surely be redundant. I will outline only a few that are of markedly increased incidence in poor children, take a deadly toll, and are obviously amenable to investigation. These include prematurity, perinatal infections (including acquired immunodeficiency syndrome), substance abuse effect on the fetus and infant, infectious diseases of early childhood (notably gastrointestinal and respiratory infections, meningitis, and measles), child abuse, trauma, homicide and suicide, teenage pregnancy, and school failure. The impact of these maladies converts potentially valuable and productive members of society into long-term financial liabilities as well as poignant catastrophes.

Each of these problems can be, and indeed must be, attacked from the research level to find a cogent solution. As an infectious disease expert, I think it is reasonable to use *Haemophilus influenzae* meningitis as an example. This is the most common type of bacterial meningitis in the young child, resulting in considerable sequelae. The incidence of this illness is markedly increased in the poor child.[1,2] The particular epidemiology of various organisms and host interactions can be discerned to determine the reasons for the increased incidence. The relationships of family crowding, day-care center care, and breast-feeding to the increased incidence of meningitis in poor children are being elucidated.[1,2]

The definition of the basic immune response on the molecular level, with particular attention given to possible immune defects in special population groups to the etiologic pathogens,[3] have spurred rational development of vaccines (as we are now seeing with conjugate polysaccharide vaccines). These are active areas of research bearing directly on this particular problem of health care for poor children. Finally, it is critical that research be conducted into systems of health care provision on a societal level that will facilitate reliable access for the poor child to the fruits of the health care system, in this case vaccine provision.

This type of investigation is not as "sexy" as dissection of molecular mechanisms, but in the broad sense is every bit as valid a research question. In this area, as in all other areas, the research must be scientifically rigorous and creative, with a mechanistic, not purely descriptive, approach. Without such research, society would deprive the most financially and health-deficient members of our population of the benefits of the more basic research advances. I have used the specific example of *H influenzae* meningitis, but equally cogent and perhaps more dramatic cases can be made for any of the problems outlined above. While some are less basic (eg, the behavioral problems) than others (eg, acquired immunodeficiency syndrome and infectious diseases), in all there is a complex and as yet poorly understood blend of basic biologic and sociopolitical issues.

Identification of the problems is the first step in finding possible solutions. To arrive at accurate solutions requires research. Again, this must include research in the broadest sense, from the molecular to the societal arena. One promising new approach is the recently established Child Health Research Centers program within the National Institute for Child Health and Human De-velopment. Seven centers were established in 1990 with the expectation of creating "centers of excellence" in a specific subject area, with considerable flexibility provided to promote the development of new pediatric investigators. Unfortunately, with the exception of this new initiative, research in general, and research into child health issues in particular, remains among the lower priorities in this country. With

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From the Division of Pediatric Infectious Diseases, University of California, San Francisco, and San Francisco General Hospital.

Reprint requests to San Francisco General Hospital, 1001 Potrero, 6E9 San Francisco, CA 94110 (Dr Kohl).

the current financial situation, there has been a progressive decline in newly funded research grants and a reduction in funding to established grants. The percentage of funded NIH grants has dropped from 62% in 1974 to an estimated 22% to 24% in 1990.[4-7] I would like to offer a list of possible solutions to these problems:

1. A basic shift in national priorities to acknowledge that the main threat to our security comes from profound internal societal problems, not external military challenges.
2. A fundamental restructuring of budgetary goals to acknowledge the change in national priorities; health care research would be placed closer to the top of the list along with other social and domestic programs.
3. Acknowledgment that problems of the poor child and child health in particular, if not addressed, will lead to crippling problems in society as the demand for productive and increasingly skilled workers accelerates.
4. With this acknowledgment, increased funding of all areas of child health problems becomes vital.
5. Recognition that funding of scientifically rigorous, creative, and mechanistic research into broad societal problems is as valid as research into molecular mechanisms.
6. Similarly, increased awareness in the pediatric academic world, including our medical school departments and research organizations, of the breadth of research, with rewards for the societal-oriented researcher being similar to those for the molecular scientist.
7. Creation of a cadre of pediatric scientists rigorously trained in the social sciences (eg, sociology, economics, and epidemiology) to enable them to contribute to the solution of the broad arena of medicosocial problems of the poor child through research.
8. A rational, long-term plan for stable national funding mechanisms to maintain the fragile research infrastructure, to provide a level of confidence in the research community, and to ensure a continuity of research and training of entry-level researchers.
9. Increased funding for the Child Health Research Centers to allow the opening of more than the initial seven funded centers.
10. Broadening the scope of Child Health Research Centers to include training and research on every level into the problems that affect children, and enhanced coordination of molecular and societal research efforts.
11. Enhanced cooperation among the public sectors of funding and the private sectors, including foundations and industry, regarding child health problems.

The problems we face in child health care, and child health care of the poor in particular, are immense. Nevertheless, they are every bit as amenable to solution as those involving Middle East oil or the savings and loan institutions. Indeed, health care problems will erode this nation's security as surely as will the more publicized national and international problems. The most efficient solutions to the problems of child health involve the traditional research methods focused on a broad plane. Once a reliable database is established and interventional techniques are validated, the solutions themselves can be instituted. Some believe that a conflict exists between research and health care for the poor, since each requires scarce resources. It is my contention that this nation is wealthy enough to fund both adequately once we reorder our priorities. Indeed, it will be the poor, so disproportionately burdened by ill health, who will benefit the most from the fruits of all research advances.

The theme of the 1991 Society for Pediatric Research's Presidential State of the Art Symposium (occurring at our annual meeting in May in New Orleans, La) is entitled "The Medical-Social Crisis in Child Health." The main areas discussed will include an overview of the vulnerable child, pediatric acquired immunodeficiency syndrome, substance abuse, and health care access for children. Thus, the research societies are acknowledging and beginning to come to grips with these issues. It will be up to the nation to further use the tools of pediatric research to aid in the solution of these problems.

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Serving the Underserved

Impact on Resident Education

Carol D. Berkowitz, MD

Numerous obstacles stand in the way of universal access to health care.[1,2] Some of these barriers are political, and influencing them is more problematic, slow, and subject to the climate of the time. Other aspects may be addressed by increasing the pool of physicians aware of and involved in the issues of serving the underserved.

The Ambulatory Pediatric Association (APA), under the leadership of Paul McCarthy, MD, began addressing the issue of serving the underserved in March 1990. A conference, cosponsored by the APA and the Bureau of Maternal and Child Health, was convened. Participants in the conference included nurses, social workers, and physicians, many of whom were chief residents in their respective training programs. These individuals were representative of different regions in our nation and cared for different populations within these regions. Participants were asked to address one aspect of the impact of underserved children on resident education.[3] The proceedings of this conference have been published and distributed.[4] The reasons for this focus on education were multiple. It is readily apparent that the underserved represent a diverse group, including a large portion of financially disadvantaged and/or geographically isolated children (rural and migrant workers). Care of these children, particularly the economically restricted, often falls into the bailiwick of pediatricians in training. By properly preparing these (and all) residents, not only may health care be improved for the children, but commitment and advocacy by the house staff may be encouraged. How will this be achieved? The purpose of this article is to outline the means to accomplish this end.

The APA took on as a project the development of a strategic plan regarding residency education. This plan has both short- and long-term objectives. The major short-term objective is the development of a core curriculum of fundamental knowledge, of necessary skills, and of unique techniques for resident education. Methods for curriculum implementation will also be defined.

The first curriculum category concerns what can broadly be referred to as clinical issues. First, the house officer needs to be able to identify the underserved individual and recognize the numerous barriers (ie, financial, governmental, geographic, institutional, or personal) to health care. The second clinical issue addresses the *specific* health problems of the underserved and educates individuals about diseases unique to or at higher incidence among certain populations. An example of this would be recognizing and being prepared to treat conditions such as tuberculosis, child abuse and neglect, and dental caries among migrant farm workers and their children.[5]

A third clinical issue involves the teaching of the interpersonal aspects of care, focusing on psychosocial issues and interviewing skills. The means to teach these to house officers have been eloquently addressed by Julia Hamilton, MSW, CISW, a social worker from Yale–New Haven (Conn) Medical Center.[6] Ms Hamilton teaches about the "five C" model of intervention. These five stages include caring, confrontation, creativity, culture, and closure. The stages are consecutive and developmental, and require mastery of one before proceeding to the next. They are practical and readily learned by house officers. Caring means demonstrating to the patient (by touching or through statements) that one cares. Confrontation involves open discussions with patients about their goals and expectations from the health care system. Creativity includes role modeling or reframing things for patients and their parents. Culture means being sensitive not just to ethnic differences, but to the culture of poverty. Last, closure means letting go, and allowing the family to solve its problems on its own. The goal of Ms Hamilton's five C model is to nurture the unnurtured. Intimately integrated in the clinical issues is teaching the house staff to identify strengths in families and children and to utilize these strengths while providing health care. These families can often benefit from a family systems approach.[7]

In addition to teaching the resident about clinical issues, the curriculum must also include community or environmental issues. First, one must address ecology, the relationship of the child to his or her environment, family, and the social systems that regulate his or her life. One must be knowledgeable about public laws, such as 94-142, that affect the care of children. Likewise, the physician must know about available categorical programs, such as the Special Supplemental Food Program for Women, Infants, and Children; Aid to Families With Dependent Children; and Medicaid, and help patients achieve access to these programs.[8] The issues of advocacy, ethics, and the legislative process should be addressed in a formal way. Didactic sessions, as well as opportunities to become in-

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From the Ambulatory Pediatric Association, McLean, Va, and the Department of Pediatrics, UCLA School of Medicine.

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volved in organizations geared to muster change, should be offered.

The house officer needs to be taught about the organization of health care systems. Included in this is formal instruction on practice management.[9] Residents should be given career counseling. The realities of reimbursement should be taught. Residents should be encouraged (inspired) to assume some responsibility for the health care of individuals whose major barrier is a financial one. Instruction about health care access and barriers, both financial and otherwise, should be given.

How many training programs already address these issues, and what methods are available to teaching house staff about serving the underserved? The APA is developing a questionnaire to assess the extent of such programs. It is hoped that programs with an established curriculum will make their curriculum available to others.

There are key methods in teaching residents to care for the underserved. First, institutions may develop rosters of faculty mentors, individuals who are knowledgeable about the issues of the underserved, who care for the underserved, and who are role models for young physicians. Such faculty members are often the ones who are overworked and overutilized. They often do not have time to do what they do, much less take on additional tasks as mentors. However, academic acknowledgment for their contribution would validate the importance of their role. Didactic lectures are another forum in which to teach about serving the underserved. These may be included in continuing care conferences. The continuing care clinic, for many house officers, is an excellent setting in which to recognize psychosocial and medical concerns of underserved children.[10] The five C model of intervention could be incorporated in this setting.[6] Block rotations could be developed, particularly in specific underserved communities. Institutions could develop "exchange" programs to allow for greater exposure of house staff to different underserved populations. Examples of such block rotations would include the homeless, migrant children, inner-city health care, etc. Built into these rotations, or as a separate part of the training experience, would be structured extramural experiences such as home visits, or visits to the welfare office. Such experiences are meant to help the house officer understand and empathize with the day-to-day struggle many of the underserved face.

The educational experience of working on a multidisciplinary team cannot be overstated. The purpose of such exposure is to increase the skills of the house officer through contact with individuals with greater expertise in areas such as interviewing.[11] The use of timely feedback using tools such as videotaping is also important to the teaching of communication skills.[12]

The appropriate timing of this instruction is also important. It is critical to use the orientation process to teach the house staff about the demographics of the people for whom they are caring. Likewise, a separate house staff retreat, away from the hectic hospital setting, is to be encouraged as a means to reinspire house staff and focus on these issues. The idealism of the medical student is lost (or put on the back burner) after graduation by the new demands and responsibilities of being a house officer.[13]

In addition to working toward developing a curriculum, organizations such as the APA should work to affect public policy to encourage resident education in the area of underserved children. For example, state and federal programs that would fund initiatives in resident education regarding the underserved should be encouraged. Inclusion of instruction on caring for the underserved should be a priority in all federally funded primary care programs. Primary-care fellowships with a focus on the underserved should be developed.

Likewise, financial issues related to the underserved should be addressed. Physicians need to be encouraged to join organizations that actively lobby for universal access to health care regardless of financial status. Physicians, individually and as members of organizations, should then be encouraged to support agencies (eg, the Health Resources and Services Administration and the Bureau of Maternal and Child Health) that focus on the underserved and support health policies that provide full funding or primary-care services and a full spectrum of care for the underserved. Loan forgiveness for those pursuing careers in serving the underserved should be encouraged.

The APA as an organization is firmly committed to the issue of serving the underserved. To date, the organization has held a conference exploring this issue and the impact that underserved children have on residency education. The APA has chosen to focus on teaching house staff about underserved children as one approach to combating the problem. It is both hoped and anticipated that better training of house officers will result in a pool of physicians who are not only more knowledgeable about health care issues of the underserved, but also more willing to care for such children, and serve as advocates and forces for change.

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The Challenge of Care for the Poor and Underserved in the United States

An American College of Obstetricians and Gynecologists Perspective on Access to Care for Underserved Women

Ezra C. Davidson, Jr, MD; Charles E. Gibbs, MD; Janet Chapin, MPH

• Access to pregnancy-related care for women and their infants and to reproductive health services for adolescents are significant concerns to the American College of Obstetricians and Gynecologists (ACOG). Adolescent and young adult women are among those most likely to be uninsured and lack access to health care services. Adolescent pregnancy, low-birth weight, and infant mortality remain major national burdens. The ACOG has taken the position that quality health care should be accessible to all women. The ACOG recommendations regarding health services for adolescents and the ACOG Committee on Health Care for Underserved Women's statement of principles regarding universal access for pregnancy-related care, which includes the basic scope of benefits, the characteristics of the providers, and the organization of services are described.

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In 1988, more than 794 000 women did not receive prenatal care in the first trimester of pregnancy.[1] Every year, more than 10% of all 15- to 19-year-old women become pregnant.[2] Access to care for underserved women—in particular, pregnancy-related care for women and their infants and reproductive health services for adolescents—is a significant concern to the American College of Obstetricians and Gynecologists (ACOG). More than 30 reports and policy recommendations have been published in the past 5 years alone on the subjects of infant mortality and access to pregnancy-related services.[3] Reports on adolescent pregnancy have multiplied, reflecting the concerns about pregnancies in this age group. Although some responses to the recommendations have been forthcoming at the state and federal levels, much more is needed before we will see significant improvements in health status. The time for study is past. Although we always need current data, it is time now to move forward to implement many of these recommendations.

THE PROBLEMS

Lack of health insurance decreases the likelihood that a woman will receive appropriate health care.[4] In 1985, of the women of reproductive age, 26% did not have insurance to cover maternity care, and 15% of the 3.7 million births in that year were to women with no health insurance coverage.[5]

One measure of access is entry into prenatal care. In 1988, for the nation as a whole, 24% of the women who gave birth did not receive prenatal care in the first trimester of pregnancy, and 6% received little or no care at all before delivery. For black women, the situation was worse; 40% did not receive care in the first trimester, and 11% received little or no care during pregnancy.[1]

Access to prenatal care is a major factor associated with low birth weight and infant mortality.[6] The personal and public costs of the stubbornly high percentage of low-birth-weight infants remain a national burden. The Office of Technology Assessment has estimated that a single low-birth-weight infant incurs between $12 000 to $40 000 in short-term hospital costs.[7] Handicapping conditions occur in approximately 5% to 16% of the low-birth-weight infants treated in today's neonatal intensive care units.[7] Long-term domiciliary and education costs for these disabled children are estimated at $6000 to $37 000 per year.[8]

In addition, adolescents and young adults are among the groups more likely to be uninsured for health care services. As of 1984, about one in every seven adolescents, approximately 4.5 million adolescents aged 10 to 18 years, had no health insurance coverage. Black adolescents were 63% more likely than white adolescents to be uninsured. Hispanic adolescents were nearly three times as likely as non-Hispanic whites to be uninsured. Adolescents living in families earning less than the federal poverty standard were three times more likely than their nonpoor counterparts to be uninsured.[9]

More than 6 million young adults, 26% of those 19 to 24 years old, were uninsured in 1984. Hispanic, black, poor and near poor, unemployed, and high school dropouts were among those young adults most likely to be without insurance. Three fourths of white young adults 19 to 24 years of age had private insurance compared with only half of blacks of the same age. More than 40% of Hispanics had no insurance, twice the rate of non-Hispanic

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whites.[9] One of the most troubling issues in adolescent health care is adolescent pregnancy. More than 1 million adolescents become pregnant every year in the United States.[2] The birth rate for teens aged 15 to 17 years rose in 1988 for the first time in a decade, to 33.8 births per 1000 women aged 15 to 17 years.[1] Compared with the rate in other developed countries, the pregnancy rate among American teenagers is among the highest in the world. It is twice the rate in England, Wales, and Canada, three times that in Sweden, and more than six times the rate in the Netherlands.[2]

ACOG RECOMMENDATIONS

Since 1971, ACOG has taken the position that quality health care should be accessible to all women.[10] This position was reaffirmed in a policy statement adopted in July 1988.[11] Since 1985, through its Committee on Health Care for Underserved Women, ACOG has addressed various components of the problems related to access to care. The ACOG also has a long-standing interest in the development of adequate, comprehensive, and high-quality health services for adolescents, with special reference to reproductive health services. Since 1964, ACOG has organized initiatives in the area of adolescent health. Over the years, more than 10 policy statements, as well as numerous other reports and committee statements regarding adolescent health, have been issued. In 1985, ACOG began a public education program that broke network television barriers that prevented the provision of good, reliable information on unintended pregnancy to the American public.

SERVICES FOR ADOLESCENTS

The ACOG holds the position that health services for adolescents must be broad in scope and must be provided in the context of adequate education, social services, and family support. Health education that includes education regarding sexuality and reproduction, beginning early in a child's life, is a cornerstone of effective reproductive health services.

Moreover, contraception and family planning services must be available and accessible for all women, regardless of age, whose sexual behavior exposes them to the risk of unintended pregnancy. Contraceptive services should be offered, whenever possible, in a general health care setting that includes counseling regarding psychosocial considerations and sexually transmitted diseases. Much more outreach and publicity should be undertaken to inform sexually active adolescents about the importance and safety of contraceptive use, as well as to assist them in locating and accessing services. The ACOG has called for responsible advertising of prescription and over-the-counter contraceptives and has indicated that it would be willing to work with publishers and broadcasters to make sure the advertising claims were accurate and scientifically verifiable.[12]

The ACOG endorses the programs, including those located in schools, that provide reproductive health services in areas where such services are not available and where such services have the support and input of parents and communities. These programs appear to be most effective when they are offered within a system of comprehensive health care services. One aim of such programs should be to encourage sexually responsible behavior that is both nondestructive and nonexploitive. The ACOG also supports the recommendations of the National Academy of Science's report *Risking the Future: Adolescent Sexuality, Pregnancy and Childbearing*, including the need to maintain the availability of adoption and abortion as needed options for adolescents.[13]

The issue of confidentiality has been identified by both providers and young people as having a significant impact on access to health care. This is particularly true for reproductive health services. Health professionals have an ethical obligation to provide the best possible care and counseling in response to the needs of their adolescent patients. This obligation includes reasonable efforts to encourage the adolescent to involve her or his parents in health care decisions. The support of parents can, in many instances, increase the potential for resolving the adolescent's problems on a continuing basis. The restrictive laws and regulations affecting confidentiality found in many jurisdictions are often impediments to care and need to be revised as a matter of public policy. The ACOG, in collaboration with the American Academy of Family Physicians, the American Academy of Pediatrics, NAACOG—the Organization of Obstetric, Gynecologic and Neonatal Nurses, and the National Medical Association, has developed a policy statement on confidentiality, since such assurances are essential to serve adolescents effectively. This policy statement sets forth the obligation of the providers of adolescent health care to protect confidentiality, as well as suggesting methods for clarifying the relationship to the adolescent and her or his parents.[14]

IMPROVING ACCESS TO PREGNANCY-RELATED CARE FOR UNDERSERVED WOMEN

Although access to all health services is important for women of all ages, among the most critical needs is access to pregnancy-related care. The ACOG Committee on Health Care for Underserved Women has developed a statement of principles regarding universal access for pregnancy-related care and the necessary characteristics of any legislation or plan that would provide such care.

The ACOG is aware of the importance of controlling costs, and this statement of principles regarding universal access should not be seen as a call for unrestrained spending. To the contrary, the college believes that comprehensive pregnancy-related care, appropriate to the various needs of each patient, is worth the initial costs and will contribute importantly to cost containment. For example, a good system of care will facilitate rapid and accurate evaluation of the effectiveness and the role of new technologies and therefore is likely to prevent unnecessary, expensive services. Administering authorities and financing plans for universal access need to be specified, but these issues are beyond the scope of the current development of the ACOG statement of principles.

Universal Access

Access to the full range of pregnancy-related services (see the list below) should be provided for all women and infants who live in the United States. It is important to note that these principles do not call for all women and infants to be covered under a single program, but there must be certain characteristics common to all coverage. Minimum benefits for all coverage and the eligibility requirements for any publicly funded and operated program should be established across the nation. Care must be organized and delivered in a manner appropriate for, and acceptable to, the pregnant woman and her family. Current public and private resources should be used whenever possible. Any publicly funded and operated health services must be kept entirely separate, administratively and financially, from public assistance/welfare programs.

Scope of Services in Maternal and Infant Care

The ACOG Committee on Health Care for Underserved Women has established the following list of basic elements of care to which it is particularly important to ensure accessibility. Pregnancy-related care must be understood as broad in scope and variable in intensity and complexity. To the degree that an element is needed but missing or inadequate, the care is deficient. Additional emphasis should be placed on prevention and early intervention in all services, and all services should be coordinated and linked.

Planning pregnancy, and the prevention of those pregnancies that are unplanned, is an important strategy to improve maternal and infant health. All women in the United States should have access to family planning and contraceptive services.

Additionally, ACOG actively supports individual choice in regard to abortion as a necessary and safe option for all women. This position is based on the belief that decisions concerning abortion are so bound in ethical, moral, and religious complexities, as well as other personal considerations, that they are best left to a woman in consultation with her physician. The ACOG believes that continued availability of safe, legal abortion services is essential to maternal health.

A prepregnancy-related health examination is important to identify behavioral and medical factors that require modification before pregnancy to improve outcome, such as control of diabetes or smoking cessation, and should be available to all women. This evaluation is not meant to include infertility services. Additionally, early pregnancy diagnosis facilitates appropriate and timely prenatal care and should be available.

Prenatal, pregnancy-related services should be based on risk assessment with an appropriate response and include care for new or preexisting conditions that affect the pregnancy, fetal evaluation, health and childbirth education, nutritional support and counseling, substance abuse counseling and treatment, and linkage of prenatal care and delivery.

Labor and delivery should be provided in an optimal, risk-appropriate environment, as should neonatal care appropriate to the needs of the infant. Postpartum evaluation and services, including family planning and postpartum sterilization, and infant follow-up for at least 1 year should be provided after delivery. Social services support as needed should be provided throughout the pregnancy and follow-up period.

Provider Characteristics

Providers of pregnancy-related services include health care professionals and such institutions as laboratories, hospitals, health departments, and community and migrant health centers. All providers should be licensed or certified when license is not required in their jurisdiction and subject to a quality review process involving peer review. There must be a sufficient number of providers, and they must be of the appropriate disciplines required to render all of the necessary services. The relationships between the primary and referral levels of care, and between the various disciplines involved in care, should be clearly defined in contractual documents between providers. Such agreements tend to clarify both responsibility and authority and also describe the extent to which any provider should commit resources. These contracts should contain cancellation clauses and should be renegotiated at regular intervals.

Organization of Services

Maternal and infant health services may be delivered by both private and publicly funded and operated services. There are, however, certain characteristics that are important for all components. The focus of care should be health-outcome oriented. However, outreach (recruitment) for both patients and providers should be supported financially, and undergraduate, graduate, and continuing education should be supported to provide an ongoing supply of qualified providers. Additionally, research designed to improve patient care should be identified and a suitable environment for investigation encouraged.

The organization and methods used to deliver services should be efficient and cost-effective and responsive to patient needs. Both the management and clinical components of the programs should be evaluated by means of outcome and process objectives, and these evaluation results should be used in decision making. All types of qualified health care professionals and other providers should be used, and incentives must be available to encourage the provision of services in geographic areas that are difficult to serve.

Certain administrative characteristics are important for any private or public organization or agency that pays for health services. There must be a simple, responsive, and prompt paper and reimbursement flow for patients and providers. Easy access to decision makers and clerical-level workers is essential for both patients and providers. Furthermore, reliable, sufficient, and consistent funding mechanisms must be present.

Additional characteristics apply specifically to those that are publicly funded and operated. The administrating agency should have a simple table of organization with clear lines of responsibility. Clinical expertise should be present within the senior management, with assurance of both professional and consumer input at the governance level. Where or when it is necessary to restrict the breadth or depth of the services to be supported or provided, the selection of the services included or excluded should be determined by a group including both health care professionals and lay persons. The particulars of reimbursement, quality assurance, and utilization review should be specified through a negotiated contract between the provider and the administrating authority. Health services should be completely separate from welfare services, in attitude and approach.

CONCLUSION: FUTURE ACTIONS

The ACOG will continue its organizational focus on these issues through two permanently established committees of its executive board. In 1990, a specific goal of advocacy for access to prenatal care for all women was articulated by the ACOG. A significant portion of ACOG's government relations activity focuses on improving access to quality health care. The college believes that this nation has a moral obligation to ensure health care for women and children at the most vulnerable time in their lives. Furthermore, providing effective maternal and infant care is cost-effective for our society as a whole.

Public education must continue to focus on the consequences that will result if we fail to improve the system of health care for pregnant women and infants in this country. The ACOG intends to educate its fellows about how to improve systems of health care and access to care and to solicit their involvement, in conjunction with government and other policy makers, in actively working toward these solutions.

Perhaps one of our most important activities is the recently established National Fetal and Infant Mortality Review Program. With grant support from the Maternal and Child Health Bureau, we have brought together many organizations to provide guidance and assistance to communities to identify the specific causes of fetal and infant mortality in their areas and to develop solutions targeted to those specific problems.

Several other aspects of this nation's health care delivery system must be repaired if access to care for the poor and the uninsured is to be guaranteed.

The problems regarding professional liability must be ameliorated by ensuring care for affected infants and support for their families. To promote self-discipline in the profession, there must be protection for those who participate in peer review and sanctioning activities.

In addition, difficulties surrounding referrals, transfers of high-risk patients, and the provision of consultation must be resolved in ways that both protect patients and allow physicians to provide appropriate levels of care for higher-risk patients. Furthermore, reimbursement and compensation for nurses, technical workers, and hospitals must be enhanced.

It is clear that public hospitals and health departments, which constitute only a portion of the current system, can no longer be expected to bear the major burden of providing care for the poor and uninsured without a greatly increased level of support.

It is naive to assume that one organization or group of organizations alone, such as organized medicine, no matter how well intentioned, can solve the problems of access to care. What is needed in this country, as in other countries, is leadership and the social will to make sure that universal access to care becomes a reality.

A history of ACOG activities in adolescent health care and a summary of all ACOG policies regarding adolescent health are available from the Resource Center of the American College of Obstetricians and Gynecologists, 409 12th St SW, Washington, DC 20024-2188.

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Poverty and Cardiac Disease in Children

Hugh D. Allen, MD; Kathryn A. Taubert, PhD; Richard J. Deckelbaum, MD; David Driscoll, MD;
Ann Dunnigan, MD; Samuel S. Gidding, MD; Paul Herndon, MD; Rae-Ellen W. Kavey, MD;
Charles Mullins, MD; A. Rebecca Snider, MD; William B. Strong, MD; Reginald Washington, MD

Almost 80 million children live in the United States. At least eight of every 1000 infants born each year have congenital heart defects.[1] When mortality and spontaneous defect improvement are factored into live birth data, Roberts and Cretin[2] estimated that by 1995 there will be 300 000 children under the age of 21 years with congenital heart disease; 38% will have had one or more surgical procedures. Other children will develop acquired heart disease, such as cardiomyopathies, rheumatic fever, acquired immunodeficiency syndrome with its myocarditis, Kawasaki disease, and arrhythmias. The projected incidence estimate for supraventricular tachycardia alone is between one and four per 1000.[3] Familial hypercholesterolemia will affect the future of an unknown but probably large number of children. Therefore, at least one-half million children in the United States have some form of cardiac problem.

One quarter to one third[4,5] of the more than 4 million infants born each year[6] are born into poverty. Therefore, approximately 150 000 to 200 000 children have the problems of both being poor and having heart disease. Considering the birth rate and incidence of heart disease, 8000 to 10 000 infants with heart problems will be added to this population each year. The impact of illegal immigrants on the overall population figure is unknown. Additionally, the assignment of the term *poverty* for a family of four at $12 675 is probably unrealistic; according to the National Center for Health Statistics, many families will still live in poverty even at a breakpoint of $20 000.[7] Some families with incomes greater than $20 000 live in a notch group between poverty and affordability. These groups will further inflate the numbers of poor children with heart problems.

Nearly every child who has been diagnosed as having a heart problem will require some follow-up care. In the Baltimore-Washington Infant Study, for example, among all patients with heart disease diagnosed during the 1st year of life, more than 80% required ongoing pediatric cardiology visits. Furthermore, about 50% required invasive diagnostic procedures and approximately 40% needed cardiac surgery (C. Ferencz, MD, MPH, Principal Investigator, Baltimore-Washington Infant Study, unpublished data, 1981-1987). Regardless of ability to pay, affected children require access to the pediatric cardiac health care system.

UNIQUENESS OF THE POVERTY POPULATION

Pregnant women who live in poverty have less prenatal care than affluent patients. This creates a problem for certain fetal conditions that must be detected in enough time to institute treatment that will allow fetal salvage. For example, fetal echocardiography permits the diagnosis of supraventricular tachycardia in hydropic fetuses. These can be successfully treated by administration of antiarrhythmic drugs to the mother. Otherwise the fetus could die. Detection and careful control of the diabetic mother results in less frequent occurrence of diabetic cardiomyopathy in the newborn. Maternal drug abuse and acquired immunodeficiency syndrome are both associated with poverty and with newborn cardiac disorders.[8-10]

The poor have greater exposure to certain environmental risk factors, such as lead, solvents, traffic and factory emissions, and pesticides.[11,12] They can be exposed to these atmospheric teratogens both at home and in the workplace.

The poor have a higher illiteracy rate, often have large families, and often experience difficulty accessing (or paying for) transportation to cardiac care for their children. This is especially the situation for the rural poor. The quality of the system accessed can be variable. All these factors contribute to fewer postnatal visits where early detection of cardiovascular disorders can make a significant difference in the survival rate of children who have potentially treatable lesions that are lethal if not detected and treated.

Subsequent problems of infants and older children with heart disease include availability of and receiving immunizations, proper nutrition, and ability to comply with ongoing treatment plans, including filling prescriptions. If the child with a significant cardiac defect becomes infected with, for example, pertussis, that superimposed disease could prove fatal in the already compromised patient. Children with cyanotic heart disease, those with congestive heart failure, and those being prepared for operation or who have had an operation require proper nutrition to maintain growth and to keep up with increased energy intake demands imposed by their condition. The child may receive an initial prescription provided by a cardiologist; however, access to a pharmacy or ability to afford

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From the Committee on Congenital Cardiac Defects, the Committee on Atherosclerosis and Hypertension in Childhood, and the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease of the Council on Cardiovascular Disease in the Young of the American Heart Association, Dallas, Tex.

Reprint requests to Office of Scientific Affairs, American Heart Association, 7320 Greenville Ave, Dallas, TX 75231 (Dr Taubert).

sometimes very expensive drugs necessary to control child's condition may prevent the parent from pro- ing that medication on an ongoing basis. Compliance h administration of the medication is sometimes com- mised by problems as simple as the parent's inability ead and understand the directions printed on the label. lder children in the poverty level have more risk fac- for cardiovascular disease as adults than do the af- ent. These include at least hypertension, smoking, and t. With their known increased exposure to drug abuse, y have a greater risk of endocarditis, of acquired im- nodeficiency syndrome with its myocarditis, and of ir own offspring having congenital heart disease, such hat encountered with exposure to cocaine and alcohol. eumatic fever has always been primarily considered a ease of the poor, and studies from the 1970s and 1980s tinue to show this pattern.[13-15] Recent data show that umatic fever attacks are still being reported in all areas the country.[16] Other published focal experiences have wn that numbers of cases of acute rheumatic fever are reasing at least in these areas, which may or may not rtend a national phenomenon.[17-21] Compliance with on- ing prophylactic measures for prevention of secondary acks of rheumatic fever is compromised by poverty, ac- s to medication, and understanding of the disease pro- s.

COVERAGE PATTERNS

Crippled Children's Services or Medicaid coverage is ailable to many poor children with heart disease. For ose who can afford it, insurance is available but may not granted to those with preexisting conditions. With ris- g costs of health insurance, insurance may not be af- rdable to those just above the poverty level no matter hether the condition is covered or not. Certain groups ve unique problems. These include the young adult er 21 years of age who previously had Crippled Chil- en's Services coverage but no longer qualifies because age. Another is the young adult who leaves college d/or reaches the age of 23 years and is no longer eligible r parental private health insurance coverage. If these pa- nts are faced with the need for a major intervention, ch as cardiac surgery, their lack of coverage, no matter hat profession they have entered, may move them into verty. This group was much smaller in the past because any of these children did not survive into adulthood. owever, surgical and medical advances have improved e survival and quality of life for these young adult cardiac tients, and many more will enter adulthood during the xt decades.

A notch group of those parents who do not qualify for ublic assistance yet cannot afford private insurance can similarly devastated by an expensive interventional rocedure that is considered necessary for treating their ild's cardiac condition. This sometimes presents the di- mma of either entering poverty or not treating the heart roblem.

Only 53% of the children below the poverty line are cov- ed by Medicaid for reasons of either not qualifying, not pplying, or not understanding the application.[22] Most ates limit children's Medicaid eligibility level, some to a vel as low as 14% of the poverty line.[23] Particularly af- cting the cardiac patient is that several states limit the umber of hospital days covered and/or the number of hysician visits allowed.[24]

Since the introduction of the "War on Poverty" 25 years go and the birth of Medicare/Medicaid, a dramatic but not et adequate reduction in the percentage of the elderly classified as "poor" (28.5% in 1966 to 12.4% in 1986) has been achieved.[23] During the same time span, children have formed the majority of the poverty population (the so-called new poor) and also represent the segment with the least insurance coverage.[23,25] Over 4 million children uninsured and living in poverty are not eligible for Medicaid.[26] The popular press has also recently discussed this problem. *Time* magazine reported that between 1978 and 1987, spending on programs for the elderly rose 52% while spending on children dropped 4% (October 8, 1990:41-48). It is apparent, therefore, that children have much less vocal representation and impact at the voting booth.

Children of the homeless, the migrant worker, and the illegal immigrant may have greater problems than those who have permanent shelter. These include less coverage because of their transience, variations in state Medicaid coverage, language difficulties, problems understanding the application process, and fear of discovery of their immigrant status.[4]

UTILIZATION OF THE SYSTEM

Some pediatric cardiology systems are not user friendly and can be confusing and intimidating, especially for poor patients. Difficulties can include transportation to the facility, parking or finding the right bus line, finding someone to stay with the other children at home, and coping with an inpatient environment where the child's illness already imposes confusion and anxiety. Many of these parents cannot afford food or housing for themselves during their child's inpatient stay. Furthermore, they may have no resources for the care of the children who remain at home.

Outpatient costs may be affordable for such situations as a physician visit but not for expensive testing, such as Doppler echocardiography or magnetic resonance imaging. All of these factors tend to discourage the parents from keeping return appointments, refilling prescriptions, or dealing with their child's ongoing cardiac health care needs.

There are up to 3 million homeless people in the United States. Depending on the geographic location, one third to three quarters are children.[27,28] Characteristics of this population include less use of the health care system, as eating is a higher priority; episodic usage of acute facilities when problems arise; and less follow-up care because of their mobility and difficulty in accessing a consistent system. Similarly, children of migrant workers, whether having immigrated illegally or not, do not have access to ongoing health care. Such parents do not always have a clear understanding of their child's cardiac condition, do not remember the name of their last provider, and move from community to community without carrying adequate documentation of their child's condition. This, in addition to lack of continuity of care in one location, complicates the situation for their child with a cardiac condition. Additionally, cultural differences, language difficulty, and fear of being detected as an illegal immigrant often delay or inhibit proper cardiac health care to this group. Certain hospitals, because of economic pressures, deny admission or care to these children unless an absolute and dire emergency is detected. They then force early discharge after the child's condition has been stabilized, but not necessarily when maximum benefit has been achieved.

Guidelines and handout materials are often written for those who have attained a fairly high educational level. For example, nutritional advice is sometimes aimed at the affluent but does not take into account foodstuffs available to the poor, who must be careful of every dollar spent at the supermarket.

Atherosclerotic risk factor prevention is likewise directed toward the affluent. Such physical activities as swimming or tennis almost categorically exclude the poor, who do not have access to such sports facilities. Tobacco advertising is characteristically directed at the poor. Risk factor education and implementation may be available only through the schools, but many inner-city or rural schools cannot afford to provide nutritional programs, hypertension screening, or physical education programs aimed toward improved fitness.

RESPONSE OF THE PRESENT SYSTEM

Pediatric cardiologists currently respond to these problems by availability, especially for emergencies on a 24-hour basis, writing off bills, and providing free care both in outpatient clinics and as inpatient teaching attendng physicians. Some offer flexible office hours and scheduling to meet the time constraints of working families. Many provide free or less expensive care at outlying clinics throughout their state, which are usually sponsored by Crippled Children's Services or the Bureau of Maternal and Child Health. These take the physician to the patient and often offer care that would otherwise be unavailable. Many pediatric cardiologists also provide education and exert political influence directly or through such organizations as the American Heart Association, American Academy of Pediatrics, and the American College of Cardiology. For example, the American Heart Association Schoolsite Program has presented heart health education to more than 7 million US schoolchildren.

Most pediatric cardiology programs directly include soial workers and nurse clinicians as members of the cardiac health care team. A few programs have access to patient mbudsmen and translators. Many hospitals allow rooming in and recognize and help with the other individual needs of parents.

Certain private and charitable organizations offer suport for these patients. Some of these include the Variety Club, Ronald McDonald housing programs, Children's Heart Fund, Make-A-Wish Foundation, and the businessman's Wings of Hope program, which uses unoccupied corporate jet seats to allow transportation between the child's home and a cardiac center.

CONCLUSIONS AND RECOMMENDATIONS FOR THE FUTURE

Physicians who provide prenatal, perinatal, and pediatric cardiac care must increase collaborative efforts that will lend insight into identification and care of the at-risk poverty mother at a level equivalent to that offered the affluent. Ways must be found to identify and treat the -risk pregnant woman. Strategies should be directed toard adequate nutrition, maternal diabetes detection and eatment, substance abuse prevention (including smokg), the effects of maternal age, and the influence of mulple pregnancies. Similarly, research support and actives should evaluate reasons for inadequate follow-up of poor children who have cardiac disease. This could inlude evaluation of problems with transportation, system cess, finances, and disease understanding.

The number of pediatric cardiologists in the United ates is limited. To provide the time for provision of equal and adequate care, more must be trained, and that training must be supported. Present resources should be used more discriminantly. For example, pediatric specialists (pediatricians) should be able to examine patients with chest pain and innocent murmurs and provide follow-up for patients with less significant cardiac problems, such as small ventricular septal defects, mild pulmonary stenosis, and the like. This can be accomplished by their gaining greater confidence through continuing education and experience. The medicolegal climate that currently drives pediatric specialists to refer and not to manage such conditions must be modified so that fear of inappropriate litigation is not a factor behind these actions. Likewise, patient attitudes must be modified to accept the pediatric specialist as a consultant and provider for such cases. Ancillary health personnel should be used to greater advantage for patient education, handling minor problems, writing to schools and insurance companies, and handling other paperwork that absorbs much of the pediatric cardiologist's time.

All pediatric cardiac care providers should be sensitive to the problems of the poor. Their practices should be near mass transportation. They should track their patients' follow-up appointments and treatments to assure compliance. This may be accomplished through development of computer databases that are simple enough to be used even by those of us who are not "computer literate." Printed materials and patient teaching materials should be written to the reading level and in the language understood by the patient's parent. When programs are developed that include general population strategies, such as hypertension education and treatment, those materials and programs must be critiqued by the group for whom their use is intended, and those critiques must receive an acceptable response before implementation.

Preventive programs should be coordinated through the school system. After-school care could be provided by parents and siblings from the same population, offering employment opportunities to them that would otherwise not be available. Physical activity programs should include all children without creating embarrassment for any child, even the clumsiest. Exercise should be viewed as fun, and lifelong sport activities should be taught instead of sports in which only a few will achieve success. Not every child will ultimately be a professional athlete. Cafeteria meal planning should address heart-healthy eating habits, and poor children should eat two meals per day at the school site. Cities should provide funding for health clinics based at the school. With these school health clinics, health promotion, not just disease diagnosis, should be emphasized. Children should receive anti-smoking education that is proved to be effective, and tobacco usage advertising directed toward children and the disadvantaged should be outlawed. Other community resources, such as churches and community centers, should be included in development of cardiovascular and other health strategies that will help the poor.

There must be universal access of adequate care to the child with cardiac disease no matter what the socioeconomic status. Medicaid and Crippled Children's Services eligibility and coverage must be improved. Care of those over age 21 years who had heart problems as children must receive continued funding similar to that provided to patients with cystic fibrosis or hemophilia. Private insurance carriers may wish to consider strategies to cover this group, which might include making a general insurance pool available to all with cardiac disease. If no private solution to the problem is forthcoming, a national health insurance alternative may be the only answer.

These children do not have a voice in politics. The effects of that lack are apparent as their general support has declined despite increases in other segments of the population. These children must be treated fairly, and it is up to us as their providers to be an effective political voice that will be heard on their behalf.

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The Challenge of Caring for Indigent Children With Rheumatologic Diseases

Michael L. Miller, MD, Patience H. White, MD

• Poverty and lack of insurance prevent complete access to tertiary care for many children with rheumatologic diseases. Long-term solutions to provide community based support for local teams and other services are needed. Physicians need to work with colleagues in health care systems and government to make the health care system fully available to all families. Medical schools can act as catalysts in helping government agencies redefine policies to support outreach and other health care programs for the indigent. Governmental agencies must collaborate with insurance companies to change policies so as to cover all aspects of service, including those provided by arthritis health professionals. With coordinated effort, the goal of adequate services to indigent children with rheumatologic and other chronic illnesses can become reality.

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Poverty amplifies problems that rheumatologic diseases impose on children and their families. Providing adequate care becomes a challenge for society no less than for physicians and other health care professionals. For the many indigent children with these diseases who do not receive continuing primary care, access to pediatric rheumatology centers becomes difficult. Those who do get to pediatric rheumatology centers often have difficulty in getting prescribed services, such as physical therapy. As a result, potentially reversible problems, such as joint contractures, may last well into adulthood; persisting disability can interfere with the ability to work. This article will examine problems with access to and delivery of care for impoverished children with rheumatologic diseases. We will suggest some approaches health care professionals can take in dealing with these problems.

PROBLEMS IN ACCESSING CARE

Poverty and lack of insurance prevent access to tertiary care for many children with rheumatologic and musculoskeletal diseases. Among youths aged 19 to 24 years, these illnesses account for more than half of chronic disabilities in this country; 20% of affected children are uninsured.[1] For the uninsured, the Medicaid program has yet to live up to its promise. Although it increased access to ambulatory services for children of lower socioeconomic status, Medicaid has covered less than half of children from low-income groups during the past decade.[2] This may explain why indigent children with health problems do not visit physicians as often as those from higher socioeconomic groups.[3,4] Because their parents cannot afford it, many indigent children with chronic diseases do not receive continuing primary care.[5] Thus, impoverished children with arthritis often cannot get longitudinal monitoring of their illness. The result can be delayed diagnosis and later referral to pediatric rheumatology centers, which can affect prognosis.

Even when Medicaid or insurance companies cover rheumatologic illnesses, many children cannot get the coordinated services they need for optimal care. Federal and state governmental agencies do not pay for all the necessary care. Those indigent families with some form of health insurance are usually underinsured because their employers offer benefits programs that do not provide full coverage. As health care costs increase, coverage becomes even more restricted. Reimbursement for physical and occupational therapy, nutritional counseling, and orthotic devices is either insufficient or, in some cases, nonexistent. Families with marginal incomes often cannot afford to pay for uncovered services.[5]

Decreased access to care for indigent children with chronic rheumatologic diseases causes serious consequences. Families experience fragmentation of services: they may need to choose between paying for primary preventative care locally or for transportation to and care at tertiary care centers. Decreased services can lead to uncorrected disability that worsens over time. Community-based services could provide some of these services if they were more complete. Respite programs offering parents help with affected children and their siblings are only partially funded.

Impoverished children with arthritis face additional problems when they enter the adult world. Young adults may lose funding for medical care because of age limits set by state agencies. Those on the lower end of the socioeconomic scale tend to have lower educational achievements. In adults with rheumatoid arthritis, low educational levels correlate with worse prognosis[6]; the resulting disabilities make getting work more difficult. Available jobs often do not offer adequate health insurance, perpetuating the cycle of decreased access to health care.

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From the Department of Pediatrics, University of Texas Health Science Center, San Antonio (Dr Miller); and the Department of Pediatrics, Children's National Medical Center, George Washington University, Washington, DC (Dr White).

Reprint requests to Department of Pediatrics, UTHSC, 7703 Floyd Curl Dr, San Antonio, TX 78284 (Dr Miller).

Thus, indigent young adults who are poorly educated may have the most severe disease and the last access to health care.

SERVICES THAT ARE NEEDED FOR OPTIMAL CARE

For children who regularly visit pediatric rheumatology centers, prognosis depends on the nature of their illness and the availability of medical services. The three most common rheumatologic illnesses of childhood are juvenile rheumatoid arthritis (JRA), systemic lupus erythematosus, and dermatomyositis.[7] Juvenile rheumatoid arthritis is not rare; in the United States, it is estimated to affect more than 10 children per 100 000.[8] Juvenile rheumatoid arthritis is classified into systemic, pauciarticular, and polyarticular types, based on clinical presentation, including number of joints affected, and course. Patients with JRA need close monitoring of their anti-inflammatory medications. They also need close follow-up by ophthalmologists, physical and occupational therapists, and other health care professionals. Lupus, an autoimmune disease of unknown etiology, can present at any age, but most pediatric cases occur in adolescent girls. Services needed depend on complications, which include chronic renal disease, pleuritis, pericarditis, and arthritis.

Patients with systemic lupus erythematosus often require chemotherapeutic agents, necessitating regular hospitalization and outpatient follow-up. Dermatomyositis, an inflammatory disease of skin and muscle, requires intensive physical therapy and anti-inflammatory or immunosuppressive medication. Most pediatric rheumatologic patients survive into adulthood. Because their illnesses often remain active, they need complex transition services. These include identifying primary care physicians familiar with their type of illness, training in job readiness skills, and sex counseling (as many are at risk for teenage pregnancy).

No matter what their socioeconomic status, children with rheumatologic illnesses and their families need help in using disparate resources scattered throughout the community. This is often best done in a planning process called "case management" by pediatric rheumatology teams. The coordinating team often includes parent representatives, physicians, nurses, social workers, and physical and occupational therapists. Team members also use their individual skills to provide coordinated care in a single setting. For instance, children and their families need to comprehend clearly the nature of their illness. Nurses help families to understand further the information communicated by other health care professionals. Families can then select from the many materials (including videotapes, pamphlets, and coloring books) now available on JRA and other rheumatologic diseases. Nurses are often the first to help families decide whether a visit to the primary physician or subspecialist is needed. In this sense, pediatric rheumatology nurses perform triage as important as that provided in emergency departments for patients with acute problems.

Indigent families need help in using resources effectively. They often do not know where to find local community services; they may not understand the bureaucratic processes required to maintain eligibility for aid. Social workers on pediatric rheumatology teams help families in a variety of ways, such as helping them get emergency funds to purchase food or obtain, complete, and follow up on application forms for state and federal aid. Since parents of children with chronic illnesses are more likely to divorce, social workers provide counseling for families in distress. Social workers identify and arrange intervention for children at risk for medical or physical neglect. These important services are seldom reimbursed. Yet social workers obtain clinical revenues from state and federal sources for medical care that would otherwise be unavailable.

Many children with JRA and other rheumatologic illnesses need to improve their independence by increasing joint mobility and muscle strength, obtaining adaptive aids for daily living, and learning coping skills to minimize pain. Physical therapists can help by recommending exercise programs for home and school. When joint flexion contractures develop in patients with JRA, occupational therapists can make some of the necessary splints. They also work with patients to improve activities of daily living. Occupational therapists work with school personnel to adjust schedules, giving appropriate periods for rest or for walking between classes. They monitor other changes in the school environment that will improve the student's ability to function.

Some patients with JRA have growth abnormalities,[9-11] become anorectic,[12] or are at risk for becoming malnourished.[13] These problems are exacerbated by the difficulty many poor families have in affording sufficient food to feed their children.[14,15] Dieticians on pediatric rheumatology teams document food intake and identify for the social worker which families need aid for nutritional supplements. They counsel families on how to prepare a balanced diet on a limited income.

Career maturity is often delayed in adolescents with rheumatologic diseases, compared with their nondisabled peers. It is most severe in those teenagers whose disease onset was in early adolescence.[16] In most of the United States, current services are inadequate to handle this group of chronically ill and disabled adolescents. For example, a recent Harris poll found that between 50% and 75% of young adults with disabilities are jobless; 67% of those who were unemployed wanted to work.[17] However, the Federal Vocational Rehabilitation System only provides services to young adults over 18 years old in many states. Earlier delivery of vocational programs might help children with rheumatologic diseases make a better transition from school to work. The widespread absence of this type of program typifies some of the problems that exist in delivering services.

PROBLEMS IN DELIVERING SERVICES

Delivering services to indigent children with rheumatologic diseases is difficult. Parents may be unable to take children for physical or occupational therapy if they lack funds for transportation. Delays in insurance reimbursement sometimes prevent families ineligible for assistance from buying medications. Inadequate funding for services makes it difficult for some medical centers to recruit and keep arthritis health care professionals.

School districts in poverty-stricken areas do not always provide special education services mandated by the federal Public Law No. 94-142 (Education for All Handicapped Act, 20 USC, §1401 (1). (15)) for children with "other health impairments," including JRA.[18] Low budgets may prevent administrators from providing school facilities that have adequate access for the physically handicapped. To be able to sit in the classroom and write their assignments, some students with severe arthritis need range of motion and stretching exercises in school. However, many poor school districts cannot offer competitive salaries or fees to recruit physical therapists, even when state funds are available for therapy sessions. Children with arthritis in these districts may suffer increasing pain, weakness, or joint contractures. As a result, they miss more days of school; when in school, they have difficulty in concentrating.[19,20]

In many states throughout the country, agencies that administer the Chronically Ill and Disabled Children's Services programs encounter fiscal constraints in caring for indigent children. To meet budgets passed by cost-conscious state legislatures, these agencies sometimes must set limits on reimbursement that interfere with care for chronic illness. Limits to the number of hospital days reimbursable for rehabilitation deny some impoverished children with severe arthritis and dermatomyositis the intensive inpatient physical and occupational therapy needed for optimal recovery. Agencies in some states must also restrict the coverable diagnoses or complications to meet budgets; for instance, only musculoskeletal complications of systemic lupus erythematosus may be covered. States do not always cover costs for necessary services provided by team members. Social work services, for example, are rarely covered. Nutritional counseling for poor children may not be available in states that do not offer reimbursement. Another example of limited service for children with arthritis concerns splinting, often necessary to restore function to contracted joints. When budget crises affect state medical programs, state agencies are forced to delay reimbursements to vendors, who in turn may not honor orthotic prescriptions. Ironically, the result may be a nonbiologic seasonal variation in the duration of joint contractures, in which increases occur at the end of the state's fiscal year.

State funding problems have also affected some outreach programs, in which pediatric rheumatologists visit outlying areas. They work with locally based health care teams, which may also care for children with other chronic illnesses. The federal or private grants that start these programs are usually temporary; when support ends, local funding may not always be sufficient to maintain all the local team members. Long-term solutions to provide community-based support for local teams and other services are needed.

POSSIBLE APPROACHES

Physicians and other health care professionals have been making progress on the problems described above. Much work remains to be done by people at all levels of the health care system. Parents, community organizations, primary care physicians, pediatric rheumatologists and their teams, and medical schools all have their role to play. With coordinated effort, the goal of adequate services to indigent children with rheumatologic and other chronic illnesses can become reality.

Parents are their children's best advocates when they understand some fundamental issues about health care. Specifically, impoverished children with rheumatologic diseases will only receive services for which society is willing to pay. Enhancing those existing services that are suboptimal will require advocacy. Therefore, parents must form new coalitions with health care professionals, community agencies, and foundations in being strong advocates for government-supported services for all indigent children with chronic illnesses.

The American Juvenile Arthritis Organization (AJAO), part of the Arthritis Foundation, provides parents a forum for advocacy, education, and support. Both parents and professionals belong to and help operate AJAO. A quarterly newsletter provides information on care and research of JRA and related illnesses. Local chapters conduct camps and other activities. An excellent compendium of information about JRA is available through the Arthritis Foundation.[21]

The Arthritis Foundation is interested in new ways in which parents can get better care for their children with rheumatologic diseases. For instance, the AJAO will be starting a new program to involve parents in regionalization of services. Regionalization is described by Perrin and Ireys[5] as the establishment of regionwide standards of referral, evaluation, and care of children with chronic illnesses. The authors discuss the utility of a database that identifies medical and nonmedical resources, and they recommend a plan for regional care that includes referral mechanisms and community education.

To establish its program fostering regionalization, the Arthritis Foundation collaborated with Daniel Lovell, MD, MPH, University of Cincinnati, Ohio, in obtaining federal support from the Maternal and Child Health Bureau of the US Department of Health and Human Services. The Arthritis Foundation is establishing the National Resource Center for Childhood Rheumatic Diseases (NRCCRD). The NRCCRD will train parents to participate in support groups, become advocates for improved services, and give feedback concerning programs to health care professionals. Local Arthritis Foundation chapters will train parent-professional teams, which will in turn train parents in pediatric rheumatology centers. Indigent families can receive training directly from these teams. The NRCCRD may serve as a model for involving indigent parents of children with many other chronic illnesses in the regionalization of health care delivery.

Community organizations need to petition state legislatures and the federal government to fund services at adequate levels for children with rheumatologic and other chronic diseases. Many organizations are currently advocating improvements in health care coverage for children with chronic illnesses, including rheumatic disease. The American Academy of Pediatrics (AAP) has proposed a comprehensive health insurance plan.[22] The AAP is also collaborating with the Maternal and Child Health Bureau in developing strategies for improving community-based access to care.

Health services research has documented the need for services; communities can help investigators get funding for further research through fund-raising and legislative advocacy. Some local health departments have been successful in convincing public health degree candidates to conduct research on delivery of health care as part of their training. Local organizations can also learn more about these issues and meet some service needs by offering to place volunteers in outreach clinics for children with rheumatologic and other chronic illnesses.

Pediatricians and other primary care physicians provide critical help for indigent children with chronic rheumatologic illnesses by following up these children along with subspecialty health care teams. In clinics serving indigent areas, primary care physicians are the first to identify problems worsened by poverty. Close communication between primary care physicians and pediatric rheumatology teams allows the teams to identify which children need help with noncompliance and school problems. Primary care physicians also work closely with pediatric rheumatology teams in coordinating provision of local services for families, thus helping to reduce fragmentation.

If primary care physicians and other health care professionals need more information about pediatric rheumatologic illnesses, information is available through local itinuing medical education and AAP education pro- ms. The Arthritis Foundation and the American Col- e of Rheumatology also provide educational materials. ıddition, programs are available where health care pro- sionals can rotate through pediatric rheumatology ser- es. Informed health care professionals can work more sely with community groups, local schools, and sub- ecialty health care teams. Using limited resources, they ı make the best choices possible in upgrading local alth care delivery.

Members of pediatric rheumatology teams help provide nprehensive service to indigent children with rheuma- ogic illnesses, as mentioned above. In the future, the reased use of questionnaires will help pediatric rheu- ıtology team members evaluate and monitor the ogress of children with JRA and related diseases. A ıool questionnaire assesses the physical problems con- nting children in school and suggests solutions to these oblems.[18] The Family Environment Scale measures the ility of families to cope with emotional issues.[23] Myones al[24] have used it to study families of patients with JRA. eticians use 24-hour recall questionnaires and diet di- ies. Monitoring the functional disability caused by JRA n help pediatric rheumatology teams identify patients need of rapid services. Lovell et al[25] recently developed ıd validated a pediatric version of the Health Assessment uestionnaire used in adults with arthritis.[26] Indigent chil- en will benefit greatly; the Lovell et al instrument can onitor the ability of intervention to improve function in tuations where many complex underlying factors may ntribute to impairment.

Outreach programs are an important indicator of how refully different professionals must work together. As entioned, government or foundation sources of initial nds will not always provide continuing support. The rvival of outreach programs therefore requires that local edical and nonmedical organizations arrange for con- nuing financial support through foundations, fund- ising, and advocacy through state legislatures. During e planning stages for new outreach programs, local or- anizations, state agencies, and medical schools need to iscuss how they can best make the transition from tem- orary to permanent sources of funding without inter- upting services.

Medical schools can act as catalysts in helping govern- nent agencies redefine policies to support outreach and ther health care programs for the indigent. For example, he University of Texas, San Antonio, has begun a pro- ram for working with state health agencies in delivering are to the poor of all ages in the Rio Grande Valley. In this rogram, called the University of Texas System Valley/ Border Health Services Task Force, university health care rofessionals and administrators meet with local and state ounterparts in designing delivery systems that conserve iscal and professional resources. The collaboration be- ween university, state government, and local health departments is critical in linking primary and specialty health are in south Texas.

Children's hospitals can establish programs for adolescents with chronic illnesses that help them prepare for employment. At the Children's National Medical Center in Washington, DC, the Adolescent Employment Readiness Center offers career and academic counseling to individual teenagers. A newsletter informs adolescents and their families about career awareness and other workshops. The center also holds seminars for schools, community groups, and employers.

Economic conditions in the immediate future may require a decrease in budgets for the care of children with rheumatologic diseases. The approaches mentioned will be feasible only if financial planning is at the core of planning coordinated programs. For instance, some children's hospitals cannot afford dedicated pediatric rheumatology teams. They may be able to establish teams caring for children with related problems, such as musculoskeletal teams for children with rheumatologic and orthopedic problems. Health care teams can use computer programs to produce more efficient schedules by tracking time required to deliver services. Administrators may be able to help teams set up fiscal models. Such models could determine the most cost-effective use of community resources by families as well as by the teams.

Eliminating rheumatologic diseases through cures generated by basic research is the ultimate solution to problems worsened by poverty. Research establishing a vaccine resulted in eliminating polio as a major health problem. Similarly, etiologies and better treatment will probably be determined by studies of transgenic mice. However, the best therapy is only as good as the ability to make it uniformly available. Governmental agencies must collaborate with insurance companies to change policies so as to cover all aspects of service, including those provided by arthritis health care professionals. Physicians need to work with colleagues in health care systems, government, and the Arthritis Foundation to make the health care system fully available to all families. Educating the public about chronic illnesses in childhood will be necessary to reach this goal. Only then will children with rheumatic diseases, irrespective of their socioeconomic status, get the primary and coordinated subspecialty care they deserve.

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What Will It Take to Fully Protect All American Children With Vaccines?

Alan R. Hinman, MD, MPH

Although 95% of children have had a full course of vac-ies by the time they enter school, immunization levels iong poor inner-city preschoolers may be substantially ver. Among the factors responsible for the disparity are lack of a uniform data system to identify children who ed vaccine; missed opportunities to offer immunizations; erinterpretation of contraindications; and administrative rriers to immunization. Remedies lie in a multifaceted ap-oach: a tracking system that will prompt a reminder and en sound an alarm when an immunization is overdue; eans of informing parents, probably best accomplished by outreach worker of the same racial or ethnic background the parent; removal of administrative barriers and in-eased access to services; incentives, either positive or neg-ive, to raise the priority of immunizations; and more ed-ation for health care providers to ensure that they iderstand contraindications and do not miss opportunities offer vaccines. Other possibilities are "express lane" ser-ces to immunize all children who come to a health care ovider and the delivery of immunizations in child care ttings and in programs such as Women, Infants, and Chil-en, and Aid to Families With Dependent Children.

(AJDC. **1991;145:559-562)**

ecent newspaper and journal articles headline the continuing occurrence of measles outbreaks in this coun-y and report that a high proportion of young children are nvaccinated. At the same time, the Centers for Disease ontrol, Atlanta, Ga, describes immunization levels in chool-age children as being at an all-time high, with more ian 95% of students having records documenting receipt f a full course of vaccines. In this article, I assert that both f these seemingly contradictory statements are true, at-empt to describe some of the factors responsible for the resent situation, and consider possible remedies.

BACKGROUND

Current recommendations call for a child to receive eight lifferent vaccines or toxoids (many in combination form and ll requiring more than one dose) in a total of five visits for mmunization between birth and school entry. The basic im-nunization schedule of the US Public Health Service's Im-nunization Practices Advisory Committee is summarized in Table 1.[1] Two discrepancies between this committee's recommendations and those of the American Academy of Pediatrics Committee on Infectious Diseases (the "Red Book" Committee)[2] are that the Red Book Committee recommends two immunization visits during the second year of life (at 15 months for measles, mumps, and rubella [MMR] and *Haemophilus* b conjugate vaccines and at 18 months for diphtheria and tetanus toxoids and pertussis vaccine [DTP] and oral polio vaccine [OPV]) and also recommends that the second dose of MMR vaccine be given at approximately 12 years of age, rather than at 5 to 6 years of age, along with DTP and OPV. Thus, a child being immunized according to the Red Book schedule would have six immunization visits before school entry (and a seventh later).

Half of US children are immunized by private physicians (commonly pediatricians) as part of overall well-child preventive care. Their parents either pay for this service or have it paid for by third-party reimbursement mechanisms. The current private-sector price for the vaccines each child should receive totals $198.55; with an estimated cost per physician visit of $15, the total for full immunization would be $303.55, following the Red Book schedule.

The other half of US children receive immunizations in the public sector, often as a specific, categorical service independent of other preventive care services. Their parents do not pay for the vaccine received (which at current public-sector prices totals $92.53) but may pay a small fee for administration. These children are likely to be members of racial or ethnic minorities and to be socioeconomically disadvantaged.

Since passage of the Vaccination Assistance Act of 1962, a federal grant program, administered by the Centers for Disease Control, has provided financial and technical assistance to supplement state and local health department efforts to provide the public sector immunizations. Grant funds typically provide half of the public-sector vaccines (approximately one quarter of the national total). The level of funding for this program has increased dramatically in the past 14 years (Figure), from a low of $5 million in fiscal year 1976 to the fiscal year 1991 appropriation of $185 million. The striking increases are largely a reflection of the dramatic increases in vaccine prices and the introduction of new vaccines. As shown by the nonvaccine grant dollars in the Figure, funding for program operations (surveillance of disease and adverse events, coordination, assessment of immunization coverage, evaluation, education, etc) has not increased significantly. Grant funds have not paid for actual administration of vaccine; this typically comes from

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Table 1.—Routine Immunization Schedule*

Age, mo	Vaccines
2	DTP, OPV, HbCV
4	DTP, OPV, HbCV
6	DTP, HbCV
15	MMR, HbCV, DTP, OPV
School entry (4-6 y)	DTP, OPV, MMR

*Based on recommendations of the Immunization Practices Advisory Committee. DTP indicates diphtheria and tetanus toxoids and pertussis vaccine; OPV, oral polio vaccine; HbCV, *Haemophilus* b conjugate vaccine (the dose at 6 months of age may not be required, depending on which vaccine is used); and MMR, measles, mumps, and rubella vaccine.

local or state health department funds, although some funds from the Federal Prevention Services Block Grant, Maternal and Child Health Block Grant, or Medicaid may also be used.

Because of the existence and enforcement of laws requiring immunization before school entry in all 50 states, here is a mechanism for ascertaining with confidence the mmunization levels of 5- to 6-year-old children. For the 1989-1990 school year, more than 97% of such children had documentary evidence of having received a full course each of DTP, MMR, and OPV (Table 2), with little variation around the country. Levels nearly as high are reported rom Head Start and other licensed day-care centers, where the school immunization requirements also apply. By contrast, there is no single nationwide mechanism for monitoring immunization levels in infants and young chilren and no mechanism for requiring immunizations. In he past, the US Immunization Survey carried out by the ureau of the Census[3] was used, but it was discontinued in 1985 because of concerns about accuracy and budgetary retrictions. It is estimated that, nationwide, 70% to 80% of hildren have received a full series of individual immuniations by the time of their second birthday (a convenient measuring point), although the proportion who have reeived the full course of all immunizations is doubtless ower. However, there is marked variation around the couny. In particular, immunization levels among poor inner-city hildren may be substantially lower. A survey in early 1990 f kindergarten and first-grade public school students in ght inner-city areas (Boston, Mass; Bronx, NY; Cleveland, hio; Houston, Tex; Jersey City, NJ; Phoenix, Ariz; Pittsurgh, Pa; and Seattle, Wash) revealed that, although more an 95% had received measles vaccine by the time of school ntry, only 51% to 81% (depending on the city) had received e vaccine before their second birthday (median, 68%).[4] ome had been vaccinated only shortly before entering hool to comply with school immunization requirements d thus had been at risk of disease for several years.

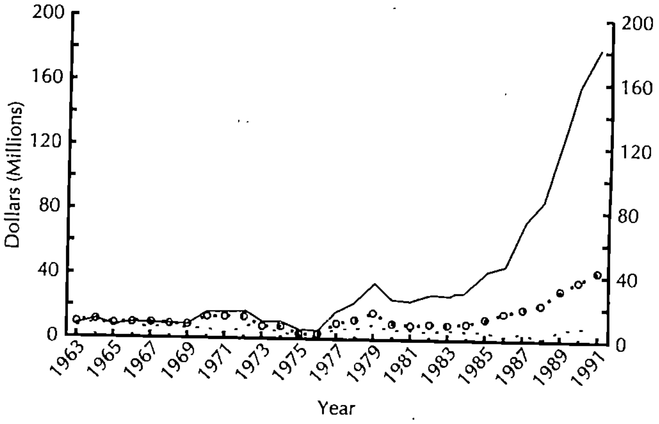
Those who are not immunized on time are likely to be embers of racial and ethnic minorities and to be socioecomically disadvantaged. A recent investigation in Chicago, demonstrated that only 50% of the students enrolled in edominantly black and Hispanic schools had been immuzed against measles by their second birthday, compared th 80% of students in predominantly white schools.[5] In edominantly black or Hispanic schools 25% to 30% of the dents had been vaccinated shortly before school entry, esumably to meet school entry criteria. An inverse correon was noted between immunization coverage by the age 2 years and the incidence of measles in preschoolers.

The striking disparity between the extraordinary sucs in assuring immunization in school-age children and unacceptable levels seen in inner-city (and in some nonurban area) preschoolers demonstrates two important facts. First, the high immunization levels in schoolchildren indicate that parents want to have (or at least do not mind having) their children immunized. Immunization ranks with motherhood and apple pie as a value for most Americans. Aggressive enforcement of the school immunization requirements, which began in the late 1970s, did not meet widespread opposition. Indeed, in Los Angeles, Calif, and New York, NY, to cite two examples, although thousands of children were denied entry to school (or were sent home) because of a lack of evidence of immunization, most returned to school within 1 or 2 days, either having found their immunization records or having been immunized.

Table 2.—Immunization Levels United States, 1989-1990 School Year*

Vaccine	Weighted Average, % Head Start	Day Care	K-1	K-12
DTP	97	95	98	98
Polio	97	95	98	98
Measles	95	95	97	98
Rubella	94	95	97	98
Mumps	97	95	98	98

*Provisional. K-1 and K-12 indicate kindergarten through first and 12th grades; DTP, diphtheria and tetanus toxoids and pertussis vaccine.



Immunization grant dollars, 1963 to 1991, including supplemental funding in 1970, 1974, 1977, 1979, and 1982; grant dollars at current value (solid line), grant dollars adjusted at the 1964 purchasing power base (broken line with circles), and nonvaccine grant dollars adjusted to the 1963 purchasing power base (broken line).

Second, the private and public "system" to deliver immunizations in the United States has the capacity to serve all children (because it ultimately does so) and that the costs of immunization in either the private or the public sector do not pose insurmountable barriers (again, because almost every child ultimately is immunized). This is not to say that the costs of immunization are unimportant; any parent would find the $59.01 (private sector) vaccine cost of the 15- to 18-month immunization with DTP, OPV, MMR, and *Haemophilus* b conjugate vaccine daunting. In fact, postponing this expenditure may contribute to the delayed receipt of vaccines. However, in the final analysis, some way is found to meet these costs.

FACTORS RESPONSIBLE

Given a willing populace and a system capable of meeting the need, why is it that we are in such trouble? Here the analysis gets softer with difficulty in documentation and in assigning weights. At least three factors seem to be involved.

Inattention by the Provider

This is a problem both in the private and the public sectors. Even though all births are registered with vital statistics authorities and more than 98% of children in this country are born in hospitals, no uniform data system keeps track of all children and identifies those in need of a dose of vaccine at a particular time. Individual physician offices may have reminder systems, but surveys of private physician records have demonstrated that 10% to 30% (or more) of their patients are not up-to-date for immunizations.[6] In the public sector, some health departments have automated systems that track individual children, identify those in need of immunizations, and may even generate mailed reminders. A few may employ outreach workers who go into the community and talk with parents about the need for immunization. In the majority of both private and public providers, however, it seems that no comprehensive system exists to identify and notify individuals who need immunization or to assess overall immunization levels in their client populations. Thus, appropriate immunization may depend on a highly motivated parent or a provider who views immunization as a priority.

Another problem arises when the provider does not review immunization status and offer needed immunizations when a child is seen for whatever reason. Each contact with the health care system should include review of immunization status and provision of needed immunizations. Other factors include excessive interpretation of contraindications to vaccination and failure to administer all indicated vaccines at a single visit. A recent review of records at a public health department child health clinic in Los Angeles revealed that only two thirds of the children received MMR vaccine on their first visit after becoming eligible (K. M. Farizo, MD, P. A. Stehr-Green, DrPH, L. E. Markowitz, MD, and P. A. Patriarca, MD, unpublished data, August 1988). None of the "missed opportunities" arose from a valid reason for withholding the vaccine.

Competing Priorities

Simply put, modern parents have many things on their minds. Many children are being raised by single parents who have jobs that do not pay well and that do not provide many benefits. In addition, other children in the home may have other problems. Thus, priorities may focus on more immediate needs, such as food, shelter, clothing, or acute medical care. "Nonurgent" issues, such as immunization of a well child, simply do not reach the threshold for action.

Another indication that immunization may not achieve high priority comes from a consideration of where (and with whom) children are during the day. Sixty percent of children younger than 5 years are in a child-care setting (including 50% of those younger than 2 years, who are most in need of immunization).[7] Of these, 31% are in a group-care setting (eg, nursery, preschool, or day-care center) where state immunization requirements may ensure immunization. As noted earlier, immunization levels in these settings are generally high. However, more than two thirds of these children (and more than 85% of those younger than 2 years) are being cared for in another setting, such as a home. Bringing these children to immunization clinics (or bringing immunization services to them) may be difficult.

Barriers to Immunization

Barriers may be as seemingly trivial as the requirement in some health department clinics that immunizations be given only by appointment rather than on a walk-in basis, or they may be more apparent, such as limited clinic hours, no evening or weekend clinics, or insufficient staff. A recent survey of state health department immunization projects revealed that 50% had such barriers.[8]

It is important that parents understand all of the benefits and risks of immunizations, and considerable effort (and legislation) has gone into trying to ensure this.[9] However, the "Vaccine Information Pamphlets" that are being developed and are required for use with all vaccines may themselves pose a barrier. Despite considerable work, they are written at an eighth-grade reading comprehension level and average 2000 words each. Given that many adults read fewer than 100 words per minute and that there will be three forms to be read at the 15-month visit (DTP, polio, and MMR), it seems likely that the process itself might be a disincentive to parents, not to mention creating an office traffic problem and tying up office staff, whose time may not be adequately reimbursed by third-party payers.

Another potential barrier is less obvious and also results from good intentions: the desire to provide comprehensive care. This may be manifested by a requirement that a child have a complete well-child appraisal before receiving vaccines. Because many health care providers (particularly in the public sector) are overextended, children must wait weeks to months for these appraisals. Meanwhile, they remain susceptible to vaccine-preventable diseases (and, in fact, may be exposed to such diseases when they visit the health care provider). This recalls Voltaire's maxim that "the best is the enemy of the good."[10]

Financial barriers may also exist. More than 15% of preschoolers are covered neither by health insurance nor Medicaid and almost 10% have no regular source of care.[11] If free public services are not readily available, these children may lose out. In addition, reimbursement mechanisms may cover acute curative care but not preventive services such as immunizations; only 45% of employment-based conventional health insurance plans covered basic childhood immunizations in a recent survey.[12]

POSSIBLE REMEDIES

The easiest recommendation is to say, "Put more resources into immunization programs." Although I agree that more resources will be required, it seems clear that money alone is not the answer.

Some have proposed that the government should provide all recommended childhood vaccines as an entitlement for all children.[13] As a lifelong advocate of immunization, I find it difficult to argue that this would be inappropriate. However, further reflection suggests that this would not solve the problem. The government (federal, state, or local) provides vaccines for socioeconomically disadvantaged children. Consequently, additional government expenditures for vaccines would essentially subsidize vaccination for the middle class and well-to-do, who seem to be getting immunized on schedule. Nevertheless, arguments have been made that free services should be provided for all, not just for the poor, so as not to establish a "two-tier" or "second-class" category of care for the disadvantaged. Another reason, given increasing vaccine costs and the increasing number of vaccines, would be to prevent diversion of private-sector patients to the public sector (where vaccines are free), thus preventing further fragmentation of care. In any event, continued government support for all recommended vaccines for socioeconomically disadvantaged children is essential.

More likely remedies flow from the factors mentioned in the preceding section. First, information systems must be developed and put into practice to (1) track the immunization status of each child, (2) prompt a reminder of needed immunizations coming up, and (3) sound an alarm when a child is overdue. Possibly even more important, such information systems would allow health care providers to assess how well they are doing in protecting their clientele. The suboptimal immunization levels found on record reviews are usually a surprise to the provider and commonly result in remedial action.

Second, effective means must be developed to get the word to the child's parents. In many areas, mail or telephone may suffice, but in many poorer areas, parents may be marginally literate, distrust official mail, or have no telephone. Direct contact by an outreach worker seems most likely to be successful in these circumstances, particularly if the outreach worker is of the same racial or ethnic background as the parent. However, additional resources would be required to fund such labor-intensive activities.

Third, some mechanism must be found to raise the priority of immunization. Mechanisms that come to mind are incentives, either positive or negative. A positive incentive might include payment (either monetary or in kind) to the parent when the child is immunized. A negative incentive might be the threat of denial of services or support if the child is not immunized. A large proportion of the children most likely to be behind schedule are enrolled in some type of public-assistance program. In four large, inner-city measles outbreaks recently investigated, it was found that of the nonimmunized children with measles who were old enough to have been vaccinated, as many as 86% were enrolled in the Aid to Families With Dependent Children program and up to 61% were enrolled in the Special Supplemental Food Program for Women, Infants, and Children.[14] Perhaps it would be possible to require age-appropriate immunization as a condition for continued participation (not initial enrollment) in these programs. Although there is justifiable concern that this might result in needy children being denied services, it seems likely that the experience encountered when first enforcing school immunization requirements would be repeated and no, or only temporary, withdrawal of benefits would occur. Additionally, such a process would also ensure that children were gotten into the health care system where they could receive other important services.

Increased efforts to promote or "market" immunizations are needed to raise the priority of immunizations.

Efforts to reduce barriers are also needed. Administrative procedures must be reviewed to ensure that they do not impede immunization. In addition, clinic services need to be increased, in terms of their overall capacity, their location, and the times at which they are offered. This strengthening of the public health "infrastructure" has historically been primarily a local and state activity, with federal involvement playing a minor role. A recent Institute of Medicine study has described the public health system in this country as being "in disarray," not just in terms of immunizations but with regard to the entire public health mandate. A societal commitment is necessary to ensure that the public sector is capable of providing needed services, and this will require increased public-sector resources from all levels.

More education is needed for health care providers to ensure that they realize the importance of immunizations, understand true and false contraindications, and eliminate missed opportunities for immunizations. Professional societies can play a leading role in this aspect.

It is not at all clear how we can reconcile the need to ensure informed participation with the fact of extensive, and often conflicting, information about the benefits and risks of particular vaccines. It is clear, however, that the days have gone of the "MDeity" deciding unilaterally what is best for the patient.

Reducing the barriers relating to the desire for comprehensive care may be difficult but should not be impossible. Even while scheduling children for future comprehensive evaluations, it should be possible to establish "express lane" immunization services to immunize all children who come to a health care provider. Leadership from professional societies will be essential to bring about this change in orientation. Immunizations should also be brought to children in child-care settings and in programs such as the Women, Infants, and Children program and Aid to Families With Dependent Children. Given the overburdened facilities of the Women, Infants, and Children program and Aid to Families with Dependent Children, the provision of immunization on site will require increased resources.

COMMENT

Although we have much to be proud of in the way we are protecting our children with immunizations, significant problems remain. No single "magic bullet" is apparent that would remove all the problems. A multifaceted approach is needed to reduce the problems already identified, and research is needed to define the factors involved in immunization and nonimmunization and to develop more effective interventions. Immunizations are among the most precious health gifts we can give our children; we must find the ways to ensure full and equitable distribution of these gifts.

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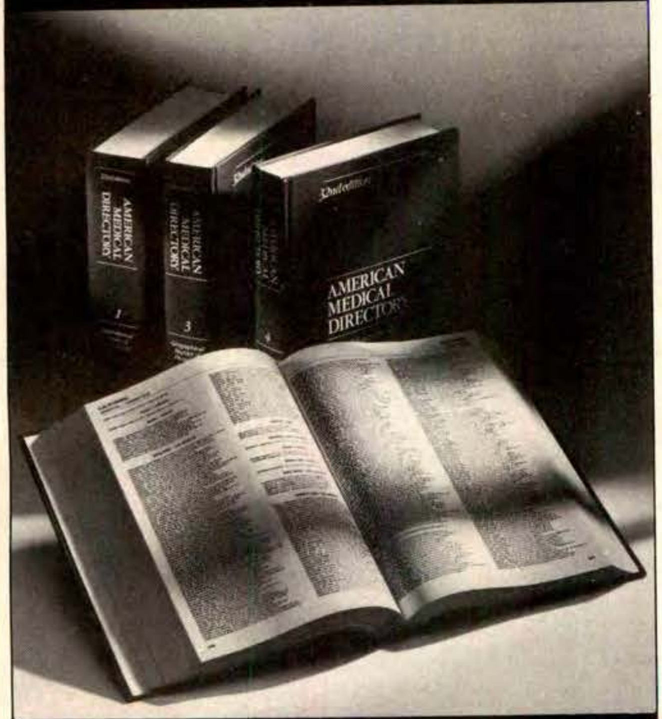

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Children's Advil®
(ibuprofen) Suspension
100 mg/5 mL

- Children's Advil® Suspension (10 mg/kg) provides better fever management than Tylenol® (10 mg/kg) in fevers above 102.5°F†[1]
- Well-tolerated in short- and long-term use[1-3]
- Prolonged duration of action…up to eight hours of relief
- Pleasant fruit flavor enhances compliance

* Tylenol® (acetaminophen) is a registered trademark of McNeil Consumer Products Company.
† Labeled fever-reducing dose of acetaminophen drops and liquid is approximately 10-15 mg/kg.
Please see following page for brief summary of prescribing information.

WYETH™ PEDIATRICS

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A NEW CHOICE
FOR PEDIATRIC CARE

Children's
Advil®
(ibuprofen)
Suspension
100mg/5mL

BRIEF SUMMARY OF PRESCRIBING INFORMATION

INDICATIONS: CHILDREN'S ADVIL® SUSPENSION is indicated for the reduction of fever in patients aged 12 months and older, and for the relief of mild-to-moderate pain in patients aged 12 years and older.

CHILDREN'S ADVIL® SUSPENSION is also indicated for relief of the signs and symptoms of juvenile arthritis, rheumatoid arthritis, and osteoarthritis.

CHILDREN'S ADVIL® SUSPENSION is indicated for the relief of primary dysmenorrhea.

CONTRAINDICATIONS: Patients hypersensitive to ibuprofen or patients with all or part of the syndrome of nasal polyps, angioedema, and bronchospastic reactivity to aspirin or other nonsteroidal anti-inflammatory agents. Anaphylactoid reactions to ibuprofen have occurred in such patients.

WARNINGS: Risk of GI Ulcerations, Bleeding, and Perforation with NSAID Therapy: Physicians should remain alert for ulceration and bleeding in patients treated chronically with NSAIDS even in the absence of previous GI tract symptoms. In patients observed in clinical trials of several months' to two years' duration, symptomatic upper GI ulcers, gross bleeding or perforation appear to occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for one year.

Except for a prior history of serious GI events and other risk factors known to be associated with peptic ulcer disease, no risk factors have been associated with increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less well than other individuals and most spontaneous reports of fatal GI events are in this population.

PRECAUTIONS: General: Because serious GI tract ulceration and bleeding can occur without warning symptoms, physicians should follow chronically treated patients for the signs and symptoms of ulceration and bleeding.

Blurred and/or diminished vision, scotomata, and/or changes in color vision have been reported. If a patient develops such complaints the drug should be discontinued and the patient should have an ophthalmologic examination.

Fluid retention and edema have been reported with ibuprofen; therefore, the drug should be used with caution in patients with a history of cardiac decompensation or hypertension.

Ibuprofen can inhibit platelet aggregation and prolong bleeding time. CHILDREN'S ADVIL® SUSPENSION should be used with caution in persons with intrinsic coagulation defects and those on anticoagulant therapy.

The antipyretic and anti-inflammatory activity of ibuprofen may reduce fever and inflammation, thus diminishing their utility as diagnostic signs in detecting complications of presumed noninfectious, noninflammatory painful conditions.

Small decreases (usually not exceeding one gram) in hemoglobin and hematocrit with an apparent dose response relationship have been observed following chronic administration. If there are no signs of bleeding, it is probably not clinically important.

To avoid exacerbation of disease or adrenal insufficiency, patients on prolonged corticosteroid therapy should have their therapy tapered slowly when CHILDREN'S ADVIL® SUSPENSION is added to the treatment program.

Aseptic meningitis: Aseptic meningitis with fever and coma has been observed on rare occasions in adult patients on ibuprofen therapy. Although it is more likely to occur in patients with systemic lupus erythematosus and related connective tissue diseases, it has been reported in adult patients who do not have underlying chronic disease. If signs or symptoms of meningitis develop in a patient on CHILDREN'S ADVIL® SUSPENSION, the possibility of its being related to ibuprofen should be considered.

Renal Effects: As with other nonsteroidal anti-inflammatory drugs, long-term administration of ibuprofen to animals has resulted in renal papillary necrosis and other abnormal renal pathology. In humans, there have been reports of acute interstitial nephritis with hematuria, proteinuria, and occasionally nephrotic syndrome.

A second form of renal toxicity has been seen in patients with prerenal conditions leading to reduction in renal blood flow or blood volume. In these patients, administration of a nonsteroidal anti-inflammatory drug may cause a dose dependent reduction in prostaglandin formation and precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, and those taking diuretics and the elderly. Those patients at high risk who chronically take CHILDREN'S ADVIL® SUSPENSION should have renal function monitored if they have signs or symptoms of azotemia. Discontinuation of nonsteroidal anti-inflammatory drug therapy is typically followed by recovery to the pretreatment state.

Since ibuprofen is eliminated primarily by the kidneys, patients with significantly impaired renal function should be closely monitored and a reduction in dosage should be anticipated to avoid drug accumulation.

Information for Patients: Physicians may wish to discuss with their patients the potential risks and likely benefits of treatment with CHILDREN'S ADVIL® SUSPENSION.

Laboratory Tests: Meaningful (3 times the upper limit of normal) elevations of SGPT or SGOT (AST) occurred in controlled clinical trials in less than 1% of patients. A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of more severe hepatic reactions while on therapy with ibuprofen. If abnormal liver tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur, CHILDREN'S ADVIL® SUSPENSION should be discontinued.

Diabetes: Each 5 mL of CHILDREN'S ADVIL® SUSPENSION contains 2.5 g of sucrose which should be taken into consideration when treating patients with impaired glucose tolerance. It also contains 350 mg of sorbitol per 5 mL. Although in clinical trials CHILDREN'S ADVIL® SUSPENSION was not associated with more diarrhea than control treatments, should a patient develop diarrhea, the physician may wish to review the patient's dietary intake of sorbitol from other sources.

Drug Interactions: *Coumarin-type Anticoagulants:* Bleeding has been reported when ibuprofen and other nonsteroidal anti-inflammatory agents have been administered to patients on coumarin-type anticoagulants; the physician should be cautious when administering CHILDREN'S ADVIL® SUSPENSION to patients on anticoagulants.

Aspirin: Concurrent use of aspirin is not recommended.

Methotrexate: In vitro studies indicate that ibuprofen could enhance the toxicity of methotrexate. Caution should be used if CHILDREN'S ADVIL® SUSPENSION is administered concomitantly with methotrexate.

H_2 Antagonists: In studies with human volunteers, coadministration of cimetidine or ranitidine with ibuprofen had no substantive effect on ibuprofen serum concentrations.

Furosemide: Ibuprofen can reduce the natriuretic effect of furosemide and thiazides in some patients. During concomitant therapy with CHILDREN'S ADVIL® SUSPENSION, the patient should be observed closely for signs of renal failure as well as to assure diuretic efficacy.

Lithium: Ibuprofen produced an elevation of plasma lithium levels (15%) and a reduction in renal lithium clearance (19%) in a study of 11 normal volunteers during the period of concomitant drug administration. Patients should be observed carefully for signs of lithium toxicity. Read package insert for lithium before its use.

Pregnancy: Administration of ibuprofen is not recommended during pregnancy or for use by nursing mothers.

Infants: Safety and efficacy of CHILDREN'S ADVIL® SUSPENSION in children below the age of 12 months have not been established.

ADVERSE REACTIONS: The most frequent type of adverse reaction occurring with CHILDREN'S ADVIL® SUSPENSION is gastrointestinal. In clinical trials among adults involving chronic administration of ibuprofen, the percentage of patients reporting one or more gastrointestinal complaints ranged from 4% to 16%.

Incidence Greater Than 1% (but less than 3%), Probable Causal Relationship (see PRECAUTIONS): Abdominal cramps or pain, abdominal distress, constipation, diarrhea, epigastric pain,* fullness of the GI tract (bloating and flatulence), heartburn,* indigestion, nausea,* nausea and vomiting; dizziness,* headache, nervousness; pruritus, rash* (including maculopapular type); tinnitus; decreased appetite; edema, fluid retention (generally responds promptly to drug discontinuation).

Precise Incidence Unknown (but less than 1%), Probable Causal Relationship (see PRECAUTIONS): Abnormal liver function tests, gastric or duodenal ulcer with bleeding and/or perforation, gastritis, gastrointestinal hemorrhage, hepatitis, jaundice, melena, pancreatitis; alopecia, erythema multiforme, Stevens-Johnson syndrome, urticaria, vesiculobullous eruptions; aseptic meningitis with fever and coma, confusion, depression, emotional lability, insomnia, somnolence; amblyopia (blurred and/or diminished vision, scotomata and/or changes in color vision), hearing loss; agranulocytosis, aplastic anemia, decreases in hemoglobin and hematocrit, eosinophilia, hemolytic anemia (sometimes Coombs' positive), neutropenia, thrombocytopenia with or without purpura; congestive heart failure in patients with marginal cardiac function, elevated blood pressure, palpitations; anaphylaxis, bronchospasm (see CONTRAINDICATIONS), syndrome of abdominal pain, fever, chills, nausea and vomiting; acute renal failure in patients with pre-existing significantly impaired renal function, azotemia, cystitis, decreased creatinine clearance, hematuria, polyuria; dry eyes and mouth, gingival ulcers, rhinitis.

Precise Incidence Unknown (but less than 1%), Causal Relationship Unknown: Dream abnormalities, hallucinations, paresthesias, pseudotumor cerebri; photoallergic skin reactions, toxic epidermal necrolysis; cataracts, conjunctivitis, diplopia, optic neuritis; bleeding episodes (e.g., epistaxis, menorrhagia); acidosis, gynecomastia, hypoglycemic reactions; arrhythmias (sinus tachycardia, sinus bradycardia); angioedema, Henoch-Schönlein vasculitis, lupus erythematosus syndrome, serum sickness; renal papillary necrosis.

*Reactions occurring in 3% to 9% of adult patients treated with ibuprofen.

OVERDOSAGE: Patients with a history of ingestion of greater than 100 mg/kg should have induced emesis or gastric lavage. Multiple dose oral administration of activated charcoal may be useful. Supportive therapy may include oxygen, respiratory support, and parenteral fluids. Because the drug is acidic and excreted in the urine, administration of sodium bicarbonate and induction of diuresis may be beneficial.

DOSAGE AND ADMINISTRATION: Fever: 5 mg/kg if baseline temperature is 102.5°F or below or 10 mg/kg if baseline temperature is greater than 102.5°F, every 6-8 hours (children); 400 mg every 4-6 hours (adults).

Mild to moderate pain in adults: 400 mg every 4 to 6 hours.
Juvenile Arthritis: 30-40 mg/kg day in 3 or 4 divided doses.
RA and OA: 1200-3200 mg per day in 3 or 4 divided doses.
Dysmenorrhea: 400 mg every 4 hours.

HOW SUPPLIED: 4 and 16 oz. bottles

Caution: Federal law prohibits dispensing without prescription.

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Improving Health Care for Underserved Infants, Children, and Adolescents

The Robert Wood Johnson Foundation's Experience

Michael P. Beachler

Improving the health care of this nation's infants, children, and adolescents has been a priority of The Robert Wood Johnson Foundation since its inception as a national philanthropy in 1972. The foundation has awarded grants totaling almost $243 million, approximately 22% of the foundation's overall grant-making to date, to programs whose aim is to improve the health of infants, children, and adolescents.

The foundation has used three major strategies in its child health efforts: service demonstrations to develop and test new models of care, research to improve the knowledge base and assess the efficacy of its service demonstrations, and training to better prepare health care providers to address common child health problems. Given the foundation's mission to improve the health care system, and particularly its long-standing interest in improving access to care, more than two thirds of its child health funding has supported service projects targeting underserved children.

The foundation's primary objective in its early years (1972 to 1980) was to increase access to personal health services. In light of the nation's high infant mortality rate, which accounted for 70% of all deaths among children under age 15 years, many of the foundation's early child health efforts emphasized improving access to perinatal care.

In the early 1980s, the foundation announced a broader agenda, one that went beyond improving access to include support of programs to help people maintain or regain maximum attainable function and to make health care arrangements more effective and affordable.

The development of its most recent child health efforts has been influenced by major changes in the organization and financing of child health services and by the changing nature of child health problems.

A CHANGING HEALTH CARE ENVIRONMENT FOR CHILDREN

With the foundation's earliest child health efforts, it was presumed that once a program was successfully implemented the health system would have sufficient resources to sustain it beyond the grant period and to replicate it more broadly. This expectation may have been appropriate in the 1970s when federal financing for child health programs was increasing, but by the early 1980s, an era of fiscal retrenchment, it was no longer realistic.

In the late 1970s, the number of children without health insurance was increasing, yet in the early 1980s public financing for child health services was cut back. From 1977 to 1985, the proportion of children younger than age 18 years without public or private health insurance increased from 17.6% to 23.4%.[1,2] Today, more than one third of the uninsured are children.

Economic changes have had a major influence on the decrease in private insurance coverage for children. For some, parents' manufacturing jobs, and accompanying health insurance, have been lost, to be replaced with service-sector jobs less likely to provide health insurance benefits. The growth of single-parent households and a reduction in the share of group health premiums paid by employers have also contributed to the decrease in private coverage.[3] Regarding public insurance, changes in Medicaid eligibility requirements reduced the proportion of low-income Americans covered from 63% in 1975 to 46% in 1983.[4] From 1978 to 1984, Medicaid expenditures (measured in constant dollars) declined 13%, and federal funding for three important sources of primary health care for poor women and children—maternal and child health services, community health centers, and health centers for migrants—declined 32%.[5]

During this period, a shift in responsibility for child health policy from the federal to the state level occurred under the Reagan administration's "New Federalism" policy. States now had primary administrative responsibility for several key child health programs, such as the Maternal and Child Health; Prevention; and Alcohol, Drug Abuse, and Mental Health block grant programs. Accompanying federal funding cuts pressured state governments to increase their support of these services. Federal Medicaid policy also started to allow states greater flexibility concerning the range of child health services they could cover and greater discretion as to who was eligible for services. In the last 5 years, Congress passed legislation allowing states to increase covered services and to provide Medicaid coverage to mothers and children without having to increase welfare payments.

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From The Robert Wood Johnson Foundation, Princeton, NJ.

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Reprint requests to The Robert Wood Johnson Foundation, PO Box 2316, Princeton, NJ 08543-2316 (Mr Beachler).

While these policy changes unfolded, the changing health problems of America's children presented significant new challenges. The premature infant of the early 1970s may have required admission to a state-of-the-art neonatal intensive care unit; by contrast, today's cocaine-addicted premature infant—in addition to neonatal intensive care—may require detoxification, foster care, and many other health and social services involving many agencies, institutions, and funding sources. The mother also requires drug treatment and help coping with an at-risk newborn. In a child health system that is fragmented and funded through a bewildering array of separate categorical programs at the federal, state, and local levels, ensuring that a child with multiple health problems obtains needed services becomes extremely difficult.

These changes in public policy, children's needs, and what are considered health-related problems have resulted in a broader focus for the foundation's programs in this area, which now concentrate on helping the child health system be more responsive to children's health needs.

SELECTED CHILD HEALTH EFFORTS

This evolution in the foundation's programs can be illustrated through brief descriptions of several of its major maternal and infant care programs. The first major initiative in this area was the Perinatal Program, an eight-site demonstration program, implemented between 1975 and 1980, designed to demonstrate the feasibility of regionalized perinatal services and to measure their impact on infant mortality and morbidity. Through this program, major medical centers worked with community hospitals to establish common perinatal risk assessment systems, maternal and neonatal transport systems, consultation and outreach education programs, and management information systems to track care. An independent evaluation of the program found that neonatal mortality rates declined by an average of 20% at the eight sites. At the same time, there was no increase in the number or proportion of infants with serious physical or developmental handicaps at age 1 year.[6] The concept of regionalizing perinatal care has taken hold strongly in most parts of the country, yet, key elements of this system—common records, training, and outreach—are not widely adopted. In fact, even former grantees have had difficulty sustaining these components of a regional system.[7]

The Rural Infant Care Program (1980 to 1985) extended this regionalized approach to isolated rural areas that had extremely high infant mortality rates. This effort supplemented the federal government's Improved Perinatal Outcomes and Improved Child Health programs. The Rural Infant Care Program mobilized 10 medical schools to provide technical support to providers in outlying communities. It also included aggressive efforts by nurses and lay outreach workers to encourage high-risk mothers to obtain prenatal care early in their pregnancies. The evaluators of the program found significantly greater reductions in infant mortality in most of the program sites compared with other rural counties in their states without this program. They also found that a significantly larger proportion of low-birth-weight deliveries in the area served were taking place in medical centers.[8] Almost all of the sites have maintained some identifiable elements of the program, although the project's interventions have not been widely implemented in other sites in these states.

By the mid-1980s, the foundation's focus had shifted. The intent of Healthy Futures: A Program to Improve Maternal and Infant Care in the South (1988 to 1992) is not to demonstrate the effectiveness of new models of care, but to encourage states and communities to incorporate what has already been learned from past demonstrations into their permanent systems of care. In contrast to the two earlier programs, in which the grantees were academic medical centers, the grantees in the Healthy Futures program are the state health departments in five southern states and Puerto Rico. (Another six sites are funded through the federal government's Healthy Generations Program, which resembles and has worked closely with the Healthy Futures program.) This S7.2-million program emphasizes promotion of regionalized systems and prenatal care outreach, improved coordination between the state's maternal and child health and Medicaid agencies, better financing for the state's perinatal care service system, and increased cooperation between public officials and private providers.

The grantees in this program have made considerable progress during the first 2 years of foundation support. For example, several states have actively promoted the adoption of uniform prenatal risk assessment tools and have improved financing (eg, expanded Medicaid eligibility, reimbursement, and perinatal service coverage).

Another example of a program developed with this broader focus is the Mental Health Services Program for Youth (1989 to 1994). Here, too, the grantees are state agencies. In this eight-site, $20.4-million program, the foundation seeks to demonstrate that through a collaborative effort between states and local communities, services for children and youth with serious mental illnesses can be organized and delivered far more effectively. Mental health, child welfare, juvenile justice, and special education agencies at the community and state levels are responsible for improving the financing and coordination of services. They also are charged with developing a continuum of mental health and supportive services to maintain seriously mentally ill children in the most appropriate settings. During the 1-year development phase of the program, each of the sites made statewide financing changes that will increase the availability of home- and community-based services.

The importance of multiple agencies and community leaders in making the child health system more responsive is also illustrated by the School-Based Adolescent Health Care Program (1987 to 1993). This 18-site, $14.5 million program is a collaborative effort involving schools, health care providers (such as hospitals or community health centers), and the community (through a formal community advisory committee). The program provides start-up support for school-based health centers that offer a comprehensive range of services in public secondary schools. The partnership between the schools and the community health providers has helped the sites secure third-party reimbursement of clinical services. In the 1989 to 1990 school year, reports Julia Lear, PhD, program codirector, more than 15 200 students received health services in the 23 schools involved, and more than 58 000 patient visits were made (oral communication, November 1990).

The foundation's most recent multi-site child health effort is a 3-year pilot test of the feasibility of restructuring publicly funded health services for children with a special emphasis on how these services are financed and delivered. It is intended to help communities simplify the complex web of categorical programs that fund services for children with many health needs and to make these services more accessible. The hoped-for result is a system more responsive to the needs of the individual child.

SINGLE-SITE PROJECTS

In addition to these demonstration programs, the foundation also supports many single-site projects funded in response to unsolicited proposals. Some of these projects also are aimed at improving children's health by making the health and social service systems more responsive.

Harlem Hospital, New York, NY, for example, has developed an injury prevention program (1988 to 1992) that mobilizes coalitions of parents and community leaders to work with representatives from the city departments of education, parks and recreation, and transportation. During the last 2 years, substantial improvements have been made in the maintenance and supervision of equipment at 28 playgrounds, and a recent hospital survey indicates that window-guard use in apartments has increased from 50% to 80% during the last few years. The hospital's childhood injury–related admissions declined by 14% from 1988 to 1989—the first recorded reduction since 1975. During the next 2 years, the injury prevention program will continue to expand the playground and window safety projects and will develop programs targeted at adolescents.

In another urban project targeting underserved children, Montefiore Medical Center, New York, NY, has developed a lead poisoning prevention and treatment program (1988 to 1992) in The Bronx that combines new services and creative financing and involves city and state social service, health, and housing agencies. The project includes community-based mobile screening and a full range of treatment. Two new services—outpatient chelation and transitional housing—will complement Montefiore's existing inpatient chelation, nutritional counseling, and after-care services. The project has already secured financing for some transitional housing from city and state housing agencies and will work with housing and Medicaid agencies to increase this capacity and secure permanent financing for the mobile screening and outpatient chelation services.

In a rural project (1988 to 1990) funded by The Robert Wood Johnson Foundation, the Freedom from Hunger Foundation is working with the Mississippi Cooperative Extension Service and the state health department to reduce nutrition-related health problems among children in the Mississippi Delta. The project is designed to integrate the nutrition education efforts of the Extension Service–administered Expanded Food and Nutrition Service Program and the state-administered Supplemental Food Program for Women, Infants, and Children (WIC). Program coordinators are training Cooperative Extension Service staff in six counties and revising policies and procedures to facilitate better coordination of the two agencies' efforts.

CHILD HEALTH RESEARCH EFFORTS

The Robert Wood Johnson Foundation's child health demonstration programs have raised many important research questions. For example, the success of the regional Perinatal Program in improving the survival of low-birth-weight infants raised the critical question of what, if anything, can be done to improve long-term health and developmental outcomes of low-birth-weight infants. In response, the foundation designed the Infant Health and Development Program (1983 to 1990), the largest randomized clinical trial of intensive early childhood interventions for low-birth-weight infants. The study principally was underwritten by the foundation with additional support from the federal government, The Pew Charitable Trusts, and Stanford (Calif) University's Center for the Study of Families, Children, and Youth. Eight cities were involved in the program: Boston, Mass; Dallas, Tex; Little Rock, Ark; Miami, Fla; New Haven, Conn; New York, NY; Philadelphia, Pa; and Seattle, Wash. The 985 children in the study sample were randomly assigned to one of two groups: children in the intervention group received home visits and were enrolled in special child development centers, with support groups for parents; children in the intervention and follow-up groups received high-quality pediatric follow-up care. The study found that children in the intervention group had significantly higher mean IQ scores and fewer maternally reported behavior problems than children in the control group. The study also provided conclusive evidence that high-quality group day care can be both safe and beneficial to low-birth-weight infants, despite their increased vulnerability to illness and their special developmental needs.[9]

Another foundation-supported child health research effort (1979 to 1983), conducted by the University of Rochester (NY) School of Medicine, assessed the effectiveness of a nurse home-visitor program for pregnant women and their infants in rural Chemung County, New York. Additional support for this project came from the W. T. Grant and Ford Foundations and the federal government. The study found that children whose families received home visits tended to have better language and fine motor skills, less use of emergency room and hospital services, and lower rates of child abuse than did children in families that did not receive these services. Home-visited mothers had fewer additional pregnancies and therapeutic abortions, were more likely to return to work, and used fewer welfare services.[10] The positive findings of this randomized controlled trial have led to a second study (1988 to 1994) to test whether the model could be replicated in an urban setting (Memphis, Tenn), again supported by multiple funding agencies, including The Robert Wood Johnson Foundation, the federal government, The Pew Charitable Trusts, the Carnegie Corporation of New York, and the W. T. Grant Foundation.

CONTINUATION AND REPLICATION

The foundation faces a continuing challenge in helping grantees identify sources of ongoing support for program services following grant expiration. Identifying such funding sources also has significant implications for whether foundation-supported programs can be replicated more broadly.

To help grantees address these issues, the foundation encourages the early involvement of potential long-term funders, sometimes through the use of declining-balance budgeting (by which foundation funds decrease over time) and matching funds requirements. In addition, several of the foundation's recent child health programs, such as the Mental Health Services for Youth Program and the Child Health Initiative, are specifically designed to encourage agencies to redeploy existing funds to maximize their impact.

Clearly, meeting the needs of underserved children and youth will remain a major and important challenge for families, the health care system, and this country. Factors such as poverty, homelessness, and family dysfunction make it difficult to address adequately the health care needs of children with complex problems, such as acquired immunodeficiency syndrome, substance abuse, and mental illnesses. For the foreseeable future, multiple organizations and constituencies, from both the health and other child-serving sectors, must be engaged in efforts to develop a comprehensive response to children's needs.

I would like to acknowledge the thoughtful contributions of my colleagues, Ruby P. Hearn, PhD, Paul Jellinek, PhD, Richard Reynolds, MD, and Steven Schroeder, MD.

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In Other AMA Journals

ARCHIVES OF INTERNAL MEDICINE

What Should We Do About HIV-Positive Health Professionals?

David M. Price, PhD
(*Arch Intern Med.* 1991;151:658-659)

The HIV-Infected Health Care Professional: Public Policy, Discrimination, and Patient Safety

Larry Gostin
(*Arch Intern Med.* 1991;151:663-665)

Care of the Poor and Underserved in America

Older Adolescents: A Group at Special Risk

Robert J. Haggerty, MD

Jeff, a 19-year-old who dropped out of school after tenth grade, has lived "emancipated" for the past 3 years on his own in New York, and survived for a time as a male prostitute. At a community health center he was recently discovered to have AIDS. When his disease progressed far enough to require hospitalization, it was found that he was ineligible for Medicaid without a prior assessment of whether his parents' health insurance covered him. But he did not want his parents to know that he had AIDS. While this may be seen as a problem with Jeff's pride, the fact that there is not presumptive eligibility for Medicaid, as there is for pregnancy, is a failure of our health system. This catch-22 situation is extreme, to be sure, but Jeff is one example of a group of poor and underserved children often forgotten by pediatricians and, indeed, by society: young people roughly 16 to 24 years of age who drop out of high school or do not go on to any further education.

The William T. Grant Commission on "Youth and America's Future"[1] labeled this group "the forgotten half." There are many other groups of children who are poor and underserved in America. Other authors in this issue address these. Older adolescents and youth are often forgotten by pediatricians and society.

Why are the forgotten half a problem today? In past decades, the majority of young people did not graduate from high school, and certainly not from college. Why are they now part of the growing population of poor and underserved young people? Because the world, especially the United States, has changed. The job opportunities for today's young workers who begin their careers with only a high school diploma or less are far more constrained than they were 15 or 20 years ago. Jobs in manufacturing that offer pay sufficient to raise a family are far less available for this group than they were 20 years ago. Unemployment for this age and educational group is high, irrespective of race, but especially for black and other minority youth. And even those with jobs have had a steep decline in income. The mean earnings of young male workers (from 20 to 24 years of age) dropped from $12 166 in 1973 to $9027 in 1984 (and the figures are probably even lower today). For those young men who are trying to head a family, the decline in earnings is striking (Fig 1, Table 1). If the family is headed by a woman or belongs to a minority group (or both), the decline in income is even greater. Between 1967 and 1986 the poverty rate among young families has doubled (Fig 2, Table 2).

The changing economy, which calls for workers in high-skill jobs rather than manual jobs, has led to a sharp increase in a new poor and underserved group.

CONSEQUENCES OF A POOR JOB MARKET

We usually do not think of the health and related problems that result from poor jobs, but they are many. Because unemployed men, or even those with full-time but dead-end jobs at minimum wage, cannot support families, young women are quite understandably reluctant to marry them. Yet given current sexual practices, they have their children. Unwed teen pregnancy can be a consequence of poor jobs. High school graduates earn more than non–high school graduates, and are more likely to be married (Fig 3). Lack of coverage by health insurance is a major problem for this age group, especially for those with low-paying and part-time jobs that traditionally offer little employee health insurance. However, these young people, when employed, earn slightly above the Medicaid eligibility level. They are in limbo regarding health insurance. One major finding of several research groups is the large number of fully employed young men who earn too little to support a family, have no health insurance, and have a high risk of health problems.

While this presents a bleak picture, we should not blame the victim. A particularly revealing finding of the W. T. Grant Foundation's Commission is that the vast majority of youth are trying to get jobs, trying to "make it" (82% of the 20- to 24-year-olds are in the work force). It is not that we have a generation of lazy workers. Young people today seem little different from those of the past. Interviews with hundreds of inner-city and rural young people in the forgotten half study demonstrate that they have the same aspirations and willingness to work as those who go on to college, but our current economy has far fewer places for such youth, and the health consequences are great.

Certainly not all cases of substance abuse, teen pregnancy, sexually transmitted diseases, acquired immunodeficiency syndrome, and low-birth-weight babies come from this group, but for a variety of reasons the risk of all of these problems is greater among the forgotten half. In addition, these problems often cluster together in the same individuals, thus geometrically compounding the problem. The medical system has greater difficulty dealing

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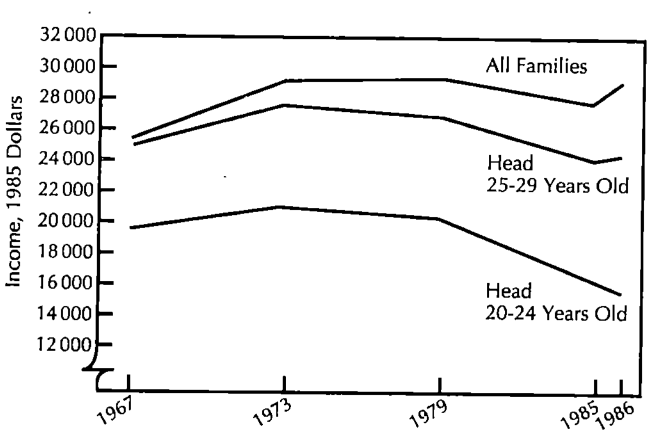

Fig 1.—*Incomes in 1985 dollars of all families and those families with heads aged between 20 and 24 years and between 25 and 29 years for the period 1967 to 1986.*

Table 1.—Trends in Real Median Incomes of Families, 1967-1986, by Age of Family Head (in 1985 Dollars)

Year	All Families	Age of Family Head, y	
		25-29	20-24
1967	25 560	25 132	19 654
1973	29 175	27 551	20 821
1979	29 028	26 676	20 025
1985	27 735	24 000	16 000
1986	28 898	24 400	15 107
% change			
1967-1973	+14.1	+9.6	+5.9
1973-1986	−1.0	−11.4	−27.4

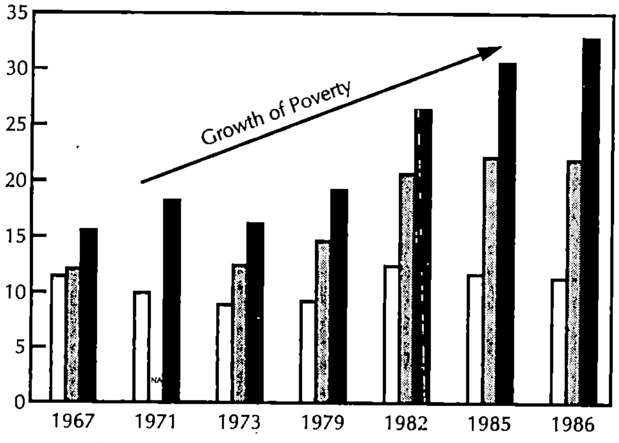

Fig 2.—*Growth of poverty in all families (open bars) and families with heads aged less than 30 years (shaded bars) and less than 25 years (solid bars) for the years 1967, 1971, 1973, 1979, 1982, 1985, and 1986. NA indicates not available.*

with these problems in people from this group, since they have so many associated social problems.

WHY SHOULD PEDIATRICIANS BE CONCERNED?

Young people 16 to 24 years of age have not traditionally been the responsibility of pediatricians. Why should we now focus on this group? I believe that pediatricians should become more involved at least with the health care of this group, and if they do, they will of necessity become involved as advocates for change in the socioeconomic and educational aspects of these young people's lives. Without such involvement, medical care by itself will be of only moderate benefit.

Table 2.—Primary Families With Income Below the Poverty Line, by Age of Family Head, 1967-1986 (in Percentages)*

Year	All Families	Age of Family Head, y	
		<30	<25
1967	11.4	12.1	15.3
1971	10.0	NA	18.0
1973	8.8	12.3	15.8
1979	9.1	14.5	19.1
1982	12.2	20.6	26.1
1985	11.4	21.8	30.2
1986	10.9	21.6	32.6

*NA indicates not available.

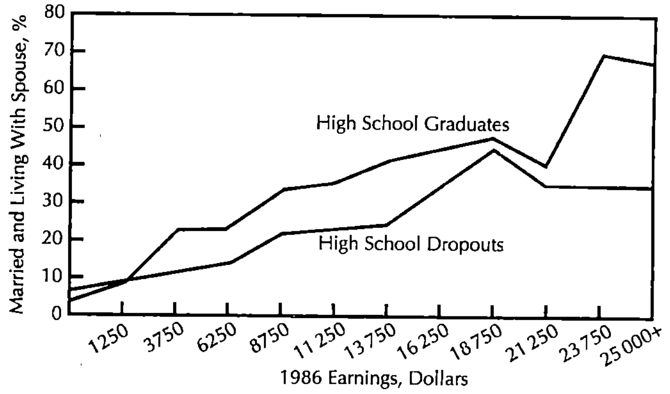

Fig 3.—*Proportion of 20- to 24-year-old men who were married and living with their spouses by 1986 annual earnings and by educational subgroup (March 1987).*

First, few other medical specialties are dealing with this age group, in part because of their lack of health insurance. Among all young people, health coverage is poor, but blacks, Hispanics, and other minorities are even less likely to have health insurance than other American youth. In 1984, 21.4% of 16- to 24-year-olds nationwide (7.4 million young people) had no health insurance, compared with 13.3% of all the civilian population.

Second, the diseases young people have are similar to those of younger children rather than being the degenerative diseases of older people that constitute such a large part of internal medical practice. Pediatricians are likely to be very competent in dealing with these health problems.

Third, no other medical specialty really specializes in all of the many interrelated problems of this age group, such as substance abuse, sexually transmitted diseases, infections, and closely related social problems. True, these problems require skills in social pediatrics, but many pediatricians are well versed in these skills. Pediatricians have generally been more involved in social action than many medical specialists.

Fourth, the field of chronic illness in this age group, while small, is especially pertinent for pediatricians. Many children with chronic childhood illnesses, such as asthma, cystic fibrosis, hemophilia, and rheumatoid arthritis, now live into their twenties. If they have been under pediatric care earlier, it makes little sense to transfer their care to another specialty when they are 16 or 18 or 20 years old, since their medical care is very similar to what it was when they were 10 years old.

Finally, we now recognize that considerable development, especially psychological, is still going on while young people are in their early twenties. Few young people take on permanently the major tasks of adulthood—family, permanent career, and citizen participation—in their early twenties. Most, especially middle-class children, try out a number of possibilities in their twenties before settling in. One of the problems of disadvantaged youth is the difficulty they have in getting second and third chances. Since understanding development is one of the pediatrician's main skills, it makes sense for us to add to our knowledge and skill to provide health care for a group of young people undergoing rapid social and emotional development in their late teens and early twenties.

WHAT CAN PEDIATRICIANS DO FOR THIS GROUP OF POOR AND UNDERSERVED CHILDREN?

At first glance, one can legitimately question whether pediatricians can do much for the forgotten half, since so many of their problems lie in the changed economic sphere. It is true that without change in job opportunities other services are going to be less than adequate. Pediatricians need to advocate promising programs in the job area, such as better vocational education programs, apprenticeship (school-job linkage) programs, educational reform that produces schools that encourage an individual's strengths and foster success, and enhanced job training partnership programs. Most of these require national initiatives and policy changes, and we can at best be supportive.

There are a number of initiatives at the local level that pediatricians can take to meet the needs of this group of poor and underserved youth. Closest to home would be to foster comprehensive service programs. Most such youth need a combination of social services, remedial education, and rehabilitation, together with medical care. Sometimes this can be organized in a group practice setting. More often the pediatrician will have to go where the young people are—the school, workplace, church, or community service center. The need for age-appropriate comprehensive services rather than any one of these services in isolation is very great. We can work toward that goal in every community.

Strengthening of families is another very important task. We often think that this age group is totally emancipated, but most still maintain contact with their parents; indeed, many remain in the parental home. Many of the young people interviewed by the W. T. Grant Foundation Commission expressed the wish to have more contact with parents and adults. Parent education programs, enhancement of parent participation in schools, involvement of parents in health programs, mentoring programs for youth, and efforts by parents, teachers, and employers to plan reasonable part-time work schedules can be done at a local level. Communities must tap the youthful energy and idealism of youth. Many youths volunteer their time to rebuild communities. Such volunteer programs have demonstrated useful ways to capture this energy of young people. For the poor, however, all of this activity cannot be voluntary. Such young people must be paid, or else they will turn to activities, legal or illegal, that yield some income. Many of the successful "volunteer" corps programs provide incentives for further education by providing an amount (usually around $5000) for each year completed toward further education. Many high school systems are now requiring a certain amount of community service as a requirement for graduation. Such service utilizes the idealism of the young, brings them in contact with adults, and gives them a true sense of value to society. One group in New York City provided an opportunity for young people to read to elderly people in nursing homes. Teachers have noticed that these young people, who could not sit still in school, became very patient and invested in their relationships with the old people. This also gave the young people a real sense of accomplishment. Every community can organize some youth activities such as these.

COMMENT

Young people in late adolescence and young adulthood, roughly 16 to 24 years of age, are a neglected group of children in our society. They are neglected by schools, health services, and employers. If they have not graduated from high school or do not go on to higher education, their future today in America is limited. They are the forgotten half. While most are energetic and ambitious, without adequate jobs to support a family, they are at increased risk of becoming single parents, engaging in substance abuse, contracting diseases, and exhibiting problem behaviors. Even those who go on to higher education often go through a period of testing alternatives in intimate social relations, jobs, and citizen roles.

A number of solutions are possible for the problems of this age group, but they require attention to programs that combine education reform, job opportunities, integrated comprehensive services, meaningful community roles, and contact with adults. Pediatricians have an important role as part of the team caring for youth, but they must also be willing to work with other disciplines in comprehensive programs and as advocates for this age group.

We may not be able to solve Jeff's problem by ourselves, but with more of the comprehensive community approaches I have outlined, we should be able to prevent many young people from reaching his state. Prevention has always been the pediatrician's main job. Now it requires social change as well as immunizations.

Some will ask, How can we convince the public of the need? People accuse me of being a congenital optimist, but I see more opportunity now than in the past 10 years. Businesses are concerned that there will not be enough skilled workers in the future. Schools are being reformed. Links between school and work are being developed. The task will not be easy, but pediatricians must add their prestige to these efforts, and join the growing chorus of those who are coming together in coalitions to make the lives of the forgotten half more healthy and effective. In so doing, they will improve the competitiveness of America in the future.

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Health Care for Pregnant Women and Young Children

Richard E. Behrman, MD, Carol S. Larson, JD

Inadequacy of family resources to purchase health care is the major reason poor, near-poor, and underserved children and youth do not obtain needed preventive, acute, and chronic health care services.[1] Other factors also can significantly limit access to health service, such as distance to facilities, availability of health providers, barriers in the organization and function of the health care system, and the attitudes and behaviors of patients.[2,3] However, inadequacy of resources to purchase medical care is the central problem. The child population whose families are unable to afford medical insurance coverage now includes 27 to 28 million infants, children, and youth who are uninsured, partially insured, or enrolled in Medicaid. The number of pregnant women who cannot afford care must also be considered when addressing the health care needs of children. Twenty-seven percent of women between ages 20 and 24 years are without private health insurance, as are 22% of teenage girls and women between ages 15 and 19 years.[3]

It is time for this country to meet the health care needs of its pregnant women and children. A strengthened partnership between the private and public sectors can meet these needs through a uniform, comprehensive, and federally initiated plan. As the debate proceeds over major restructuring of the health care system, comparatively minor changes to the current system can be made today to care for our youngest and most vulnerable population. These changes could apply immediately to pregnant women and all young children or could be phased in by birth cohorts. In the long run, the costs of providing this health care will be low compared with the health and social costs that follow in adulthood from lack of health care during early childhood.

BACKGROUND

The opportunity for many of our nation's children to fulfill their potentials as productive citizens is being severely compromised even before they reach school age. A child's capacity to thrive in later years is limited by health and developmental problems ignored in early life during the especially critical period from conception through age 5 years. This is also the period of life for which the evidence of the beneficial effects of appropriate health and developmental interventions is strongest. At any time, this most vulnerable population totals about 26 million individuals, consisting of approximately 22 million children aged 5 years or younger and 4 million pregnant women. An estimated 23% of this population are below the poverty line[4] and particularly likely to fall into a health care gap, ie, are likely not to receive important health and related services between conception and delivery (eg, prenatal care and treatment of substance abuse) and between birth and entering public programs (eg, Head Start, child care, or school, which can provide such services as immunization and screening for disabilities).[5,6]

The families of children without disabilities or illness can often bridge any gaps financially to see that their children receive the care they need. Many families cannot afford the health services their children require, however, and are ineligible for Medicaid and other programs.[3] Indeed, given the widely varying eligibility standards of Medicaid among the states, whether poor children are covered has more to do with where they live than what they need. Even families with children covered either by Medicaid or private insurance can experience tragic gaps in health care. Both public and private benefit packages are limited in coverage, and an increasing number of barriers make it more difficult to maintain coverage and obtain access to services.

Myriad proposals have emerged in recent years to reform the health system for people of all ages. Some build on the current structure; others urge a complete overhaul. They use, in different combinations, diverse strategies such as a single-payer system, managed care, and employer-mandated coverage.

The debate over health care provision in this country is not likely to be resolved quickly. Indeed, a new health care system may most likely evolve from lessons learned from relatively incremental change. If so, that change should start with pregnant women and young children. As the recent congressional expansions of Medicaid attest, there is consensus that the health needs of this population should receive high priority.

The American Academy of Pediatrics (AAP) has proposed a plan that would build on the current system to better meet the health care needs of pregnant women and children.[7] The following proposal contains many of the components of that plan and a few additional provisions: to allow a phase-in that targets young children first, to establish health providers in underserved areas, to establish a national insurance commission, to create a public/private council for citizen participation in the monitoring of health care provision, and to provide ongoing outcome measures of effectiveness.

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PROPOSAL

We propose a targeted national health care program that could be phased in incrementally over 6 years by enrolling all pregnant women and newborns each year by birth cohorts. In addition to requiring lower initial outlays, this approach would also provide an opportunity to implement a new public/private health insurance partnership program without significantly disrupting the existing complex of health care providers, payers, and employers. Furthermore, the program could be implemented on a controlled, small scale that would make it possible to troubleshoot unforeseen problems during the phase-in. This approach also takes a first step in addressing the larger health insurance problem in this country without incurring the enormous financial obligation inherent in the more global solutions that have been proposed.

The major points in this proposal are as follows:

1. All pregnant women and young children would be covered by private health insurance (indemnity or managed care) purchased through either public or private funds and consisting of a basic benefit package (including preventive health and screening programs, ambulatory and hospital care, and related social services). The health benefit package would be developed with reference to the AAP benefit list and current provisions of the Medicaid and Early Periodic Screening, Diagnosis, and Treatment program.[7]

2. All private health insurance policies and contracts would be required to include this benefit package, and a special payroll tax would be levied on employers who did not offer insurance. For children whose parents cannot afford a policy and do not receive coverage from an employer, coverage would be purchased and premiums paid through a combination of income-graduated, family payments; public funds financed by the payroll tax on employers and employees; and allocations from federal and state budgets. Payments from the latter sources might be indexed to the proportion of children under age 6 years in the state. Premiums for insurance purchased by the public fund would be negotiated with consideration of the cost of purchasing the health benefits in the marketplace and of variations in health care costs.

3. Many of the health and related services that would be required under this proposed children's health plan are currently provided for some children through a variety of federal and state programs, and these program funds would be transferred and consolidated to fund this plan. This would likely include transfers from federal programs such as Medicaid; Title V of the Social Security Act; the Supplemental Food Program for Women, Infants, and Children; and immunization grants.

4. The existing provider health provision systems would be used. The Public Health Service would be expanded and authorized to provide care in areas where numbers of health professionals are inadequate. This public program would include a voluntary program by private physicians, perhaps with subsidized professional insurance coverage or other provisions to attract these health providers. Recruitment of young physicians to the Public Health Service might also be facilitated by an educational loan forgiveness program in exchange for service.

5. Reimbursements to providers would be based on diagnosis related groups and a professional relative value system schedule developed for this population.

6. A Federal Child Health Insurance Commission would be created to establish standards and the basic benefit package, to coordinate states and their insurance commissions, and to oversee the insurance broker function and negotiation and payment of premiums. State agencies would be identified as the agents for disbursement of public funds.

7. A Council for Children's Health and Related Social Services would be established with broad representation from private and public sectors, including appropriate professionals. This council would be a national umbrella organization to advise and monitor the health delivery system. The council would have state and local units, creating a federation of local volunteer and public agencies throughout the country to assist in monitoring and coordinating outreach and volunteer efforts in health care.

The national council would be responsible for making recommendations about the basic benefit package to the federal and state insurance commissions and for monitoring the implementation of these recommendations. Its recommendations would also inform the premium negotiations.

The national council, in cooperation with the Department of Health and Human Services and state departments of health and education, would also annually review and report on the status of this insured population based on available selected health outcome measures, such as the proportion of women receiving late or no prenatal care, infant mortality, immunization rates, hospital use by children, and primary school absenteeism and performance.[8,9] This would be an important element in evaluating effectiveness of the services provided under this program and in making recommendations for change in benefits, payments, or other services.

The state and local affiliates of the council would assist in oversight and coordination of services, community innovation, and problem solving. "Lead organizations" would be selected at the state and local levels from among the private and public organizations concerned with child health and welfare. These lead organizations would be responsible for working with families, providers, and various local voluntary and public agencies to ensure that each pregnant woman and young child obtains needed high-quality services. These groups would also regularly report to the council on provider and insurance carrier performance. These reports would be incorporated into the council's recommendations to the insurance commission.

COSTS AND ADMINISTRATION

The AAP estimates that its plan to insure pregnant women and children aged 18 years and younger would increase the \$98.8 billion currently spent on this population annually to \$111.4 billion.[7] This more modest plan focusing on the youngest children would cost significantly less Because of its incremental approach and the relatively small population covered, it would facilitate the field-testing of the new administrative structures and the private-public partnership in program implementation. Thus, unanticipated problems could be better dealt with than might otherwise be possible. It would cause minimal disruption in the insurance industry and various provider systems.

CONCLUSION

Initiating change in the current system would be less costly than maintaining the status quo. Failing to provide preventive health and early treatment services results in larger direct and indirect costs to society than providing services early in life. In addition, the costs of such a program are probably lower than one might assume because most members of this population are healthy. The costs of providing health services for all children and pregnant women account for a relatively small portion of total national health care expenditures.

To address the health needs of this overlooked group in a cost-efficient way, we need to elicit significant efforts from local private and public sectors and from the federal government. All share in the potential benefits when these children succeed in becoming productive citizens.

Failure to address the health needs of today's children is having insidious consequences for our society, causing uncertainty and suffering for our families and compromising our future productivity and competitiveness.[6,9] Our future will be mortgaged to a much greater extent by this negligence than by failure to reduce the federal budget deficit. The proposed program would start to address this problem by focusing on pregnant women and young children, those whose health needs are not only great, but also will have consequences for the well-being of this country for decades to come.

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Article

Children's Services in an Era of Budget Deficits

Barbara B. Blum, Susan Blank

It is virtually impossible to address the issue of how to improve the care of the nation's poor children without confronting the question of the resources society is willing to spend on those children. As a first step in examining that question, I suggest we visualize an increasingly common sight in contemporary hospitals: a premature, low-birth-weight infant, born with medical complications and hooked up to a life-support system. The baby's mother is penniless; the hospital, or, in other words, society at large will spend thousands of dollars to give the infant all the medical assistance he or she needs to breathe and eat and develop.

What the scenario tells us is that in this instance, society has concluded that almost no amount of money is too much to spend to save the life of a child. The statement is a powerful one. Granted, the work of the neonatal care unit reflects society's stake in preserving any human life, but it is fair to say that commitment assumes a special force and urgency when its subject is a *young* life. The resources we devote to premature infants born into poverty suggest that we honor the potential to develop and grow in any child, however frail or disadvantaged.

But that commitment to children has its limits. If we pursued it to its logical conclusion, we would not live in a society that cares for the baby until he or she can leave the neonatal unit and then allows the infant to go home to an apartment infested with rats. When the infant reaches school age, we could not be satisfied to let the child begin an education in a badly overcrowded and dilapilated building where it takes years to fix a leaky roof. We would also not be able to live with the fact that the emergency department will be that child's only source of health care.

Clearly, almost no one actively endorses such a level of risk to children's health and development, yet childhood deprivation persists and worsens. One reason is the isolation of poor children. Despite growing attention to childhood poverty in the United States, many low-income children live in neighborhoods separated from a mainstream society that reads about them in newspapers but does not personally witness their plight.

Another reason for the neglect of children is the racism and classism that pervade a supposedly egalitarian society. Racism and classism make it easier to ignore children in poor neighborhoods; indeed, racism and classism may even make it more attractive to care for babies in the highly technological professionalized neonatal environment than in the communities to which they return.

However, efforts to make poor children more visible to the public at large will be of little consequence unless underlying questions about resources can be answered. Growing state and federal budget deficits confront children's advocates with a seemingly open-and-shut objection to greater investments in services. Children do have unmet needs, concede the budget cutters, but there is simply no more money. Government, they contend, is in much the same position as a poor family that needs every penny to make it through the week. When short-term budgets are tight, long-term prevention gets defined as a luxury.

For the family, pinched resources manifest themselves as hesitating to take a child to the doctor until an illness grows sufficiently serious to require treatment in the emergency department. For society, budget constraints mean spending more on shelters and welfare hotels after people become homeless than on raising the public assistance allowance, or they mean providing expensive neonatal care to some women because prenatal care is not universally available. Just as the family scrapes enough together to buy a used car, but has nothing left for its upkeep, so society funds the popular Head Start program but dissipates its gains by failing to provide the high-quality education that would reinforce the enriched early childhood experience. Scarce resources must be reserved for averting or alleviating crises; prevention and long-term maintenance are worthy but unattainable luxuries. These principles, argue supporters of fiscal austerity, are as true for government as they are for families.

However persuasive, the analogy is flawed. A wealthy society with its government in budget straits is not the same as a family in budget straits. The government simply has more choices. To pay for better services to meet children's basic needs, this wealthy nation can raise taxes. Used for better prenatal care or drug treatment for pregnant addicts or decent housing allowances, the resources would be money well spent.

At this juncture, however, another set of objections to investing in services must be confronted. There are two meanings to the phrase "money well spent," and we have thus far focused only on the first, the sense that resources will be used for worthwhile ends. When the services are better health care, housing, and early childhood education, their value is easy to defend. It is the second meaning of "money well spent," the concept of *money used efficiently*, that raises more difficult questions.

The source of the difficulty is that as currently structured, our human services system does waste resources.

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To a degree, the problem is the one already discussed: the overemphasis on costly crisis intervention at the expense of prevention. However, the crisis mode is not the only source of inefficiency. Another is the lack of accountability for public funds spent on human services. The problem is familiar. A program is launched, funds are allocated, and, once established, the program continues to receive support year after year. The principal measure of the program's performance is whether it follows certain procedures. Too little effort is made to find out whether the program is making a difference for children and families. As the public sees it, tax dollars disappear into a void.

In fact, considerable progress has been made on this front, and to a certain extent public perceptions have not caught up with what has been accomplished. We must recognize that this country is the beneficiary of more than a decade of large-scale experimental research efforts that have used controlled studies to measure the effects of various programs. Even when it is impossible to conduct sophisticated treatment/control group studies, as is the case with most programs, officials recognize more and more the value of regularly examining indicators on families at risk. In the absence of controlled studies, it is of course impossible to know precisely how much change can be attributed to particular interventions and how much to external factors. Nevertheless, as new programs are tried, indicators do offer practitioners, policymakers, and the public a general sense of whether initiatives are moving in the right direction.

One of the many examples of this new interest in program accountability comes from the Council of Governors' Policy Advisors (formerly the Council of State Policy and Planning Agencies), an affiliate of the National Governors' Association, which, in the summer of 1990, completed what it calls a Policy Academy on children and families at risk. The academies are intensive technical assistance conferences for teams of top state officials who meet to develop a plan for solving complex policy problems. The teams taking part in the recent academy series on children and families devoted a great deal of time to the issue of how to gauge the success of the plans they developed by examining changes in specific indicators, such as rates of low-birth-weight infants or of teen pregnancy. We need to infuse much more of the planning associated with human services with this approach, which moves beyond mechanistic, procedural measures of how a program functions to a more probing assessment of whether it seems to be effecting change.

Another, still more fundamental source of inefficiency in the way money is spent to help families is the very structure of the country's health and human services systems. These systems are both overly centralized and fragmented. Multiple agencies with multiple funding streams are charged with specialized responsibilities for serving the same families. These families are neither equipped nor inclined to sort through their life problems and fit them into boxes constructed by government. Consequently, they often do not know which agency they should approach for help. When they do locate the right system, they often discover that services are offered only at central, inconvenient locations.

Families pay a high price in frustration and discouragement when they try to negotiate the service maze. Society pays a high price when the maze keeps multiproblem families from getting access to the help they need, thereby allowing their problems to worsen. Government wastes precious resources in duplicative intake processes and reporting requirements and in the time and energy spent piecing together funds from different sources to support single programs.

How should the system function? There are a variety of ways to conceptualize what reform would look like. Many of us who are familiar with social services in New York City like to point to an exemplary program, the Center for Family Life in the low-income community of Sunset Park, Brooklyn, to illustrate what could be done. The center, which is supported by a mixture of private and public funding sources, is open to any family in the neighborhood with children. Through the center, families have access to a rich array of services, including a therapeutic nursery program, job search assistance, parenting education, and many others.

Regardless of the reason why someone first walks through the center's door, staff members are always alert to other kinds of help that that person *and* his or her family may need. While a child may enroll in the center's afterschool program, the mother may later avail herself of its counseling services, turn to its employment program for help in finding a job, and, as she comes to feel at home, bring her whole family to its community dinners. The center client, say its staff, is typically not an individual, but the entire family. Every effort is made to avoid artificial distinctions between, for example, "child welfare families," "substance abusing families," and "families receiving public assistance." Instead, the criterion for service is, What help does the family need to function well?

Around the country are hundreds of local programs that share the center's vision of holistic services. They operate with many different funding sources, from many different bases, serving many kinds of families and communities. However, the efforts of these innovative community-based programs are overshadowed by the large public bureaucracies that poor families must typically turn to for assistance. The question is, can these bureaucracies possibly be reconfigured so that the maze becomes a neighborhood center? The center would be friendly and convenient, its mode of operation would be to keep a limited number of staff members closely and continuously involved with one family, and, finally, it would give the family easy access to many different kinds of key services, such as income and housing assistance, preventive health care and child welfare programs, employment and training initiatives, and drug treatment programs.

In New York City, where children's advocates have repeatedly called for integration and decentralization of publicly funded services for poor families, there is now some ground for optimism. A project called Agenda for Children Tomorrow (ACT), which was privately initiated but is now supported in part by the mayor's office, is beginning to map service needs and usage patterns in 10 of the city's poorest neighborhoods. The mapping is the first step in a plan to build a neighborhood-based service system in these districts and eventually throughout the city. It will take time, patience, skill, political commitment, and a generous portion of good luck to create coordinated community services in New York City. However, those of us who have been involved with ACT are gratified that at last a systematic effort to realize the vision is under way.

Local reform efforts like ACT, however, cannot proceed in a vacuum. Initiatives to reconfigure services at the community level are much more likely to succeed if they enjoy a supportive policy environment at the state and national levels. Unfortunately, the federal environment often chills nd constricts, rather than nurtures, state and local experimentation. As with almost all generalizations, this one demands qualifications. First, most federal officials want o foster flexibility. However, legislative and institutional practices frequently obstruct that good impulse. Second, some developments of the 1980s, including, for example, he use of block grants or the new latitude given to states o create their own welfare-to-work programs, did favor service coordination. Too often, however, the freedom given to states and localities by the federal government was undercut by funding cuts and freezes. More imporantly, despite block grants and special programs that encourage coordination, state and local officials are still met at every turn with federal policies that encourage them to hink categorically rather than holistically. We need to look no further than the Congressional committee structure for n example of this problem.

Congressional staffers, when approached with ideas for new federal initiatives that crosscut conventional program reas, typically acknowledge that the House and Senate ommittee structures are hurdles that must be surmounted if more integrated programs are to be authoized. Because Congress should serve as an aid, not an obstacle, to decategorization, careful thought is needed bout how to rationalize the way the committees do business.

At best, however, improvements will be very gradual. Thus, we must also consider if there are ways to give states more immediate relief from the constraints of federal policies. One answer may be to modify the assumptions that nderlie decisions about whether to grant states waivers or federal regulations on programs for children and famies—to presume that states should be permitted flexibily in following the rules established for categorical fundng unless there is good evidence to the contrary.

A starting point for this more short-term reform might e to look into the work of a panel that until recently was nown as the Low Income Opportunity Control Board. stablished in 1987 under the White House Office of Policy Development, the panel has been renamed the Economic mpowerment Task Force and will operate under the diection of Housing Secretary Jack Kemp. The task force is n unusual federal entity in that it brings together assistant ecretaries from the wide range of departments that overee social welfare programs. Its mission is to examine ideas or state-sponsored demonstrations—programs estabshed for the purposes of evaluation—and a key element f that work is to review state requests for waivers to conuct them. With representatives from all the agencies from which a state would be likely to need waivers, the board ffers a shortcut to states that would otherwise need to pply to multiple agencies to launch a complex demonration.

The board's new name and leadership suggest there is robably federal interest in broadening its authority to ake advantage of its unusually wide-ranging represention. There are several good possibilities for such an exansion. Perhaps the task force could become more proctive in encouraging states to undertake demonstrations. lso, rather than confining itself to demonstrations, the sk force could also simplify the waiver process when ates wish to apply for experiments that involve admintrative, nonresearch activities. In addition, the rule now ollowed by the task force that waivers will be approved nly for demonstrations that are revenue neutral should e modified. Because this stipulation ignores the start-up osts associated with almost all demonstration programs, places unnecessary restraints on experimentation.

Expanding the functions of the task force is one possible route that the federal government could take to make it easier for states to innovate; there are clearly many others that would likewise offer states greater flexibility in the use of funds, leaving them in a stronger position to support locally based, coordinated services.

States, however, do not inherit all their problems in this area; some are indigenous. Like the federal government, states have legislative committees that carve the needs of high-risk families into pieces that are difficult to fit together. Similarly, states have their own centralized bureaucracies that take too many decisions out of the hands of communities.

There are, however, signs of change. In many ways, states are now exploring possibilities for restructuring. For example, the American Public Welfare Association has formed a commission of top state welfare and child welfare officials to recommend reforms in the child welfare system, and that group strongly supports the creation of a more integrated service system for children and families. Efforts to build integrated family services are already under way in Iowa and in states taking part in a special child welfare initiative sponsored by the Annie E. Casey Foundation.

In addition to the federal and state policy environments, a third sector of our society, the professional community, must change if more efficient and helpful local service systems are to be developed. The challenge to professionals has two dimensions, each reflecting one of the two structural problems in contemporary health and human services systems discussed earlier: their fragmentation and overcentralization.

First, to heal the system's fragmentation, the psychologist, child welfare worker, nurse, and many other professionals must be willing to move outside the confines of their own disciplines. The social worker cannot become a public health specialist, but perhaps he or she can become more attuned to the way the public health specialist views families and their needs. The employment specialist need not be a child welfare worker, but perhaps he or she should become more conversant in the language that child welfare workers speak.

Second, to decentralize systems and make them more accessible to clients, professionals must be willing to hand some of the control they now exercise over to local leaders and, ultimately, to families. Families must have a choice in the way services are designed, provided, and prioritized. If they say they prefer family day care to center-based programs, if they believe the neighborhood needs drug treatment more than recreational services, and if they conclude that a single mothers' group established for parenting education purposes should focus less on child-rearing and more on how to find a job, then professionals should listen.

In fact, many professionals are beginning to collaborate across disciplines and shape programs in response to what families themselves say they need. In some cases, these professionals have the wholehearted backing of their agencies, but, overall, more top-down institutional support is needed for this kind of innovation.

In addition, workers must be *trained* to function in a more multidisciplinary system. On-the-job innovation is heartening, but many of the fresh approaches now being taken by health and human service professionals ought to become the standard practice taught to students before they begin their careers. Equally important is orienting current workers to the challenges and demands of coordinated and locally based service provision.

Because there is a tendency to oversell every solution to poverty problems in this country, we should be well aware that, however desirable, a more coordinated and decentralized service system is no panacea. First, while coordination should save precious resources, it will also require new investments in the short run. Changing service systems requires planning, training, and consulting, and none of these activities is without its price tag.

Second, and even more critical, is the fact that clustering services and even clustering them in neighborhoods is likely to be a necessary but insufficient step to bring about the full measure of systemic change that should occur. Services can be integrated, but if they are of poor quality or if there are simply not enough of them, little has been gained.

On the other hand, the potential benefits of coordination are undervalued if there is an assumption that the *way* in which services are provided has little or nothing to do with their *substance*. In fact, the kind of reconfiguration discussed here could improve the quality and possibly even the quantity of family interventions. Convenient, accessible services provided by workers who think about the needs of the entire family constellation would axiomatically be better services. As to the question of supply, if integration reforms created systems that made more sense to workers and families than do current arrangements, the improved morale could, in turn, help to convince the public to invest the dollars needed to create a decent supply of services for children at risk.

Perhaps it is idealistic to expect that the country can create a new and vital service system during the next 10 to 20 years, but there are times when idealism is the only appropriate response to reality. In 1991, when large numbers of children are vulnerable to poverty, homelessness, ill health, and developmental disabilities, it is time, if not past time, for bold and creative systemic change.

In Other AMA Journals

ARCHIVES OF NEUROLOGY

Corpus Callosotomy for Intractable Seizures in the Pediatric Age Group

Richard E. Nordgren, MD; Alexander G. Reeves, MD; Adele C. Viguera; David W. Roberts, MD (*Arch Neurol.* 1991;48:364-372)

The Caring Program for Children

The Michigan Experience

Marianne Udow, MHSA; Vernon K. Smith, PhD; Margaret H. Mason, MHSA

• Public-private partnerships may offer the best opportunity in the near-term for addressing the problem of the uninsured. In Michigan, a broad spectrum of groups has studied the issue of the uninsured and, despite the diversity of the groups, arrived at a consensus that providing coverage to uninsured children is an urgent priority. The Caring Program for Children, a private program initiated by Blue Cross of Western Pennsylvania to provide primary and preventive health care coverage to children in low-income, uninsured families, gained support from the Michigan legislature and advocacy and provider groups as a means to address the problem. Blue Cross Blue Shield of Michigan and the Michigan Department of Social Services joined to expand the Caring Program for Children from a private program to a public-private venture funded by federal and state funds and private donations that has the potential to provide coverage to more than 12 000 children. The Michigan experience may be instructive to other states attempting to devise immediate local solutions to the problem of the uninsured.

(*AJDC.* 1991;145:579-580)

Health care financing and delivery mechanisms used in other industrialized nations have been suggested by many as models for reform of the American health care system. Given the pluralistic nature of American politics, however, it is unlikely that approaches used by other countries can be successfully duplicated in this country. At least in the near term, reforms that build on the current system rather than necessitating radical restructuring of existing mechanisms are most likely to garner sufficient support to be implemented. We describe one approach to building on the current financing and delivery mechanisms to address issues of access to care. Implications for broader applicability are also considered.

The Caring Program for Children (CPC) is a well-established private program offering health benefits to uninsured children who meet eligibility criteria. The program was initiated by Blue Cross of Western Pennsylvania and implemented in 11 additional Blue Cross and Blue Shield plans throughout the country. While the programs have provided health benefit coverage to some children who are not eligible for other private or public programs and whose families cannot afford private insurance, as a private effort the programs have had relatively modest impacts on the problem of uninsured children. In Michigan, the Department of Social Services (DSS) and Blue Cross and Blue Shield of Michigan (BCBSM) have worked together to expand the CPC into a public-private partnership plan. This effort will be a laboratory to test the effectiveness of combining federal, state, and private funding to offer health benefits through a private delivery and administrative mechanism.

BACKGROUND

Across the United States over the last half decade, key state and local policymakers have become involved in efforts to identify the number of uninsured Americans and to devise local strategies to address the problem. Some states have initiated programs ranging from universal access models and mandated employer-based health coverage to initiatives that target specific population groups.

There is no "silver bullet" approach toward which policymakers automatically migrate as each state grapples with the need to strike a balance between cost and coverage. Common to all the states' efforts, however, is that diverse groups and coalitions have developed consensus on the urgency of the local situation and that the solutions reflect the unique circumstances and conditions each locality. The recent Michigan experience illustrates how coalitions can develop to create a policy environment conducive to implementation of programs that address health care for the uninsured.

In the middle to late 1980s, the increasing priority given to health care of the uninsured in Michigan was reflected in the creation of task forces, commissions, and work groups by provider, advocate, and health policy organizations. In Michigan, this included The Greater Detroit Area Health Council, the Michigan Hospital Association, the Michigan State Medical Society, the Michigan Protection and Advocacy Service, and the Michigan League for Human Services. Remarkably, given the diversity of the groups examining the issue, a sense of urgency about the creation of programs to provide health care for children was common among all groups. The findings that one third, or about 300 000, of the uninsured in Michigan are children—most of them in families of the "working poor"—and that uninsured children in need of medical care do face severe obstacles to obtaining care, generated consensus that any strategy should include as its first priority a focus on children. All who studied this issue concluded that neither private nor public approaches alone

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From Blue Cross and Blue Shield of Michigan, Detroit (Mss Udow and Mason) and the Michigan Department of Social Services, Lansing (Dr Smith).

Reprint requests to Blue Cross Blue Shield of Michigan, 600 Lafayette E, J218, Detroit MI 48226 (Ms Mason).

will solve this problem, but that a combination of public and private approaches will be necessary.

For example, based on the findings of the Governor's Task Force on Access to Health Care, a broadly representative, 40-member body, "Healthy Start" was proposed as an expansion of Medicaid to provide health care coverage to children up to age 18 years in families with incomes of up to 200% of the federal poverty level. At the same time, BCBSM announced plans to implement the CPC, to be financed by private donations. The DSS and BCBSM began discussing ways to work together to ensure that the programs would be complementary.

Meanwhile, two legislative committees were examining the issue of the uninsured. The House Republican Task Force on Affordable Health Care for the Uninsured included in its final report,[1] issued in July 1990, eight recommendations largely focused on making health insurance more affordable to small-business owners. Notably, the primary recommendation was that legislation should be enacted to allow BCBSM to implement the CPC. The House Democratic Commission on Families identified health care as one of the key issues affecting the strength of families and urged in its September 1990 report[2] that priority be given to the adoption of statutory changes necessary to implement the CPC.

Owing to other budget priorities, Healthy Start was not enacted by the 1990 state legislature. The DSS and BCBSM then joined forces and secured a 3-year, $6.6 million matching grant from the Health Care Financing Administration to supplement private and state funds for the CPC. Underlying the grant proposal was the premise that through public-private partnerships programs such as the CPC are greatly enhanced—use of public funds allows the Michigan CPC to provide coverage to more children and broaden benefit coverage, while use of private sector delivery mechanisms offers access to more providers. The federal grant allowed the CPC to expand coverage to include prescription drugs, and the program has the potential to provide coverage to more than 12 000 children.

PROGRAM DESIGN

The CPC is designed to provide the highest priority services to the population group with the greatest need for health care services.

Administrative Structure

Blue Cross and Blue Shield of Michigan provides free administrative services, and the DSS administers the funds and assists with outreach and coordination with government programs. To ensure broad community involvement in the program, an advisory committee composed of 30 representatives from business, labor, religious organizations, the health care providers, parents, and state government provides fund-raising, outreach support, and general oversight of the CPC.

Target Population

The CPC provides primary health care coverage to children aged 18 years and younger whose household incomes are at or below 185% of the federal poverty level and who are not eligible for Medicaid or other sponsored health coverage. Under the terms of the Health Care Financing Administration grant, priority for coverage is given to children of employed former welfare recipients. All eligible children in a family are required to enroll simultaneously to provide a mixed risk pool of sick and well children. Enrollees are recertified annually.

Benefits

Benefits under the CPC are aimed at providing the basic preventive and primary health care coverage children need to avoid chronic illness and permanent disability. Because children are hospitalized less often than adults, and to provide coverage for as many children as possible, inpatient care is not covered under the program. Benefits of CPC include preventive care (including well-child care and immunizations), office visits to physicians, outpatient and office diagnostic and therapeutic laboratory and radiology services, outpatient and office surgery and anesthesia, outpatient and office accident medical emergency care, outpatient substance abuse services, and prescription drugs. These are covered in full, with no deductibles or copayments.

Provider Arrangements

All BCBSM participating physicians and BCBSM Participating Provider Organization pharmacies are eligible for reimbursement through the CPC. A number of pediatricians, family practitioners, and other providers are participating with BCBSM especially for the CPC.

Funding

The CPC is supported by private funds raised by BCBSM and state funds, which are matched by a special grant from the federal government. Private contributions to the program are tax deductible.

IMPLICATIONS

While the Michigan CPC is only a relatively small step toward providing health benefit coverage to the uninsured, it can have profound lessons for a more comprehensive solution. First, the program is easily duplicated in other states. Second, existing structures necessary to implement the program are for the most part already in place so that implementation can occur relatively quickly. Finally, the program builds widespread coalition support. Indeed, the strength of this effort has been the broad base of interest from providers and consumers of health care as well as from private health benefit carriers, financiers, regulators, and legislators. The depth of this support, including the willingness to commit to this effort on a long-term basis, will be key to the general applicability of this kind of an approach.

In the long term, more radical restructuring of our mechanisms to finance health care may be necessary to ensure access to health care for all. It does not appear, however, that this country is yet ready for such a major change in health policy. In that context, much can be learned from the several efforts under way across the country that use public-private partnerships to deliver health care services to segments of the uninsured populations. Programs that can be implemented now and that maximize funding and administrative capabilities from all sources, such as the Michigan CPC, are likely to have much more immediate impacts on delivering needed care to the uninsured.

References

1. House Republican Policy Committee. *Recommendations of the House Republican Task Force on Affordable Health Care for the Uninsured.* July 1990.

2. The House Majority Commission on Families. *Interim Report.* September 1989.

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BRIEF SUMMARY OF PRESCRIBING INFORMATION

INDICATIONS: CHILDREN'S ADVIL® SUSPENSION is indicated for the reduction of fever in patients aged 12 months and older, and for the relief of mild-to-moderate pain in patients aged 12 years and older.

CHILDREN'S ADVIL® SUSPENSION is also indicated for relief of the signs and symptoms of juvenile arthritis, rheumatoid arthritis, and osteoarthritis.

CHILDREN'S ADVIL® SUSPENSION is indicated for the relief of primary dysmenorrhea.

CONTRAINDICATIONS: Patients hypersensitive to ibuprofen or patients with all or part of the syndrome of nasal polyps, angioedema, and bronchospastic reactivity to aspirin or other nonsteroidal anti-inflammatory agents. Anaphylactoid reactions to ibuprofen have occurred in such patients.

WARNINGS: Risk of GI Ulcerations, Bleeding, and Perforation with NSAID Therapy: Physicians should remain alert for ulceration and bleeding in patients treated chronically with NSAIDS even in the absence of previous GI tract symptoms. In patients observed in clinical trials of several months' to two years' duration, symptomatic upper GI ulcers, gross bleeding or perforation appear to occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for one year.

Except for a prior history of serious GI events and other risk factors known to be associated with peptic ulcer disease, no risk factors have been associated with increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less well than other individuals and most spontaneous reports of fatal GI events are in this population.

PRECAUTIONS: General: Because serious GI tract ulceration and bleeding can occur without warning symptoms, physicians should follow chronically treated patients for the signs and symptoms of ulceration and bleeding.

Blurred and/or diminished vision, scotomata, and/or changes in color vision have been reported. If a patient develops such complaints the drug should be discontinued and the patient should have an ophthalmologic examination.

Fluid retention and edema have been reported with ibuprofen; therefore, the drug should be used with caution in patients with a history of cardiac decompensation or hypertension.

Ibuprofen can inhibit platelet aggregation and prolong bleeding time. CHILDREN'S ADVIL® SUSPENSION should be used with caution in persons with intrinsic coagulation defects and those on anticoagulant therapy.

The antipyretic and anti-inflammatory activity of ibuprofen may reduce fever and inflammation, thus diminishing their utility as diagnostic signs in detecting complications of presumed noninfectious, noninflammatory painful conditions.

Small decreases (usually not exceeding one gram) in hemoglobin and hematocrit with an apparent dose response relationship have been observed following chronic administration. If there are no signs of bleeding, it is probably not clinically important.

To avoid exacerbation of disease or adrenal insufficiency, patients on prolonged corticosteroid therapy should have their therapy tapered slowly when CHILDREN'S ADVIL® SUSPENSION is added to the treatment program.

Aseptic meningitis: Aseptic meningitis with fever and coma has been observed on rare occasions in adult patients on ibuprofen therapy. Although it is more likely to occur in patients with systemic lupus erythematosus and related connective tissue diseases, it has been reported in adult patients who do not have underlying chronic disease. If signs or symptoms of meningitis develop in a patient on CHILDREN'S ADVIL® SUSPENSION, the possibility of its being related to ibuprofen should be considered.

Renal Effects: As with other nonsteroidal anti-inflammatory drugs, long-term administration of ibuprofen to animals has resulted in renal papillary necrosis and other abnormal renal pathology. In humans, there have been reports of acute interstitial nephritis with hematuria, proteinuria, and occasionally nephrotic syndrome.

A second form of renal toxicity has been seen in patients with prerenal conditions leading to reduction in renal blood flow or blood volume. In these patients, administration of a nonsteroidal anti-inflammatory drug may cause a dose dependent reduction in prostaglandin formation and precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, and those taking diuretics and the elderly. Those patients at high risk who chronically take CHILDREN'S ADVIL® SUSPENSION should have renal function monitored if they have signs or symptoms of azotemia. Discontinuation of nonsteroidal anti-inflammatory drug therapy is typically followed by recovery to the pretreatment state.

Since ibuprofen is eliminated primarily by the kidneys, patients with significantly impaired renal function should be closely monitored and a reduction in dosage should be anticipated to avoid drug accumulation.

Information for Patients: Physicians may wish to discuss with their patients the potential risks and likely benefits of treatment with CHILDREN'S ADVIL® SUSPENSION.

Laboratory Tests: Meaningful (3 times the upper limit of normal) elevations of SGPT or SGOT (AST) occurred in controlled clinical trials in less than 1% of patients. A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of more severe hepatic reactions while on therapy with ibuprofen. If abnormal liver tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur, CHILDREN'S ADVIL® SUSPENSION should be discontinued.

Diabetes: Each 5 mL of CHILDREN'S ADVIL® SUSPENSION contains 2.5 g of sucrose which should be taken into consideration when treating patients with impaired glucose tolerance. It also contains 350 mg of sorbitol per 5 mL. Although in clinical trials CHILDREN'S ADVIL® SUSPENSION was not associated with more diarrhea than control treatments, should a patient develop diarrhea, the physician may wish to review the patient's dietary intake of sorbitol from other sources.

Drug Interactions: *Coumarin-type Anticoagulants:* Bleeding has been reported when ibuprofen and other nonsteroidal anti-inflammatory agents have been administered to patients on coumarin-type anticoagulants; the physician should be cautious when administering CHILDREN'S ADVIL® SUSPENSION to patients on anticoagulants.

Aspirin: Concurrent use of aspirin is not recommended.

Methotrexate: In vitro studies indicate that ibuprofen could enhance the toxicity of methotrexate. Caution should be used if CHILDREN'S ADVIL® SUSPENSION is administered concomitantly with methotrexate.

H_2 Antagonists: In studies with human volunteers, coadministration of cimetidine or ranitidine with ibuprofen had no substantive effect on ibuprofen serum concentrations.

Furosemide: Ibuprofen can reduce the natriuretic effect of furosemide and thiazides in some patients. During concomitant therapy with CHILDREN'S ADVIL® SUSPENSION, the patient should be observed closely for signs of renal failure as well as to assure diuretic efficacy.

Lithium: Ibuprofen produced an elevation of plasma lithium levels (15%) and a reduction in renal lithium clearance (19%) in a study of 11 normal volunteers during the period of concomitant drug administration. Patients should be observed carefully for signs of lithium toxicity. Read package insert for lithium before its use.

Pregnancy: Administration of ibuprofen is not recommended during pregnancy or for use by nursing mothers.

Infants: Safety and efficacy of CHILDREN'S ADVIL® SUSPENSION in children below the age of 12 months have not been established.

ADVERSE REACTIONS: The most frequent type of adverse reaction occurring with CHILDREN'S ADVIL® SUSPENSION is gastrointestinal. In clinical trials among adults involving chronic administration of ibuprofen, the percentage of patients reporting one or more gastrointestinal complaints ranged from 4% to 16%.

Incidence Greater Than 1% (but less than 3%), Probable Causal Relationship (see PRECAUTIONS): Abdominal cramps or pain, abdominal distress, constipation, diarrhea, epigastric pain,* fullness of the GI tract (bloating and flatulence), heartburn,* indigestion, nausea,* nausea and vomiting; dizziness,* headache, nervousness; pruritus, rash* (including maculopapular type); tinnitus; decreased appetite; edema, fluid retention (generally responds promptly to drug discontinuation).

Precise Incidence Unknown (but less than 1%), Probable Causal Relationship (see PRECAUTIONS): Abnormal liver function tests, gastric or duodenal ulcer with bleeding and/or perforation, gastritis, gastrointestinal hemorrhage, hepatitis, jaundice, melena, pancreatitis; alopecia, erythema multiforme, Stevens-Johnson syndrome, urticaria, vesiculobullous eruptions; aseptic meningitis with fever and coma, confusion, depression, emotional lability, insomnia, somnolence; amblyopia (blurred and/or diminished vision, scotomata and/or changes in color vision), hearing loss; agranulocytosis, aplastic anemia, decreases in hemoglobin and hematocrit, eosinophilia, hemolytic anemia (sometimes Coombs' positive), neutropenia, thrombocytopenia with or without purpura; congestive heart failure in patients with marginal cardiac function, elevated blood pressure, palpitations; anaphylaxis, bronchospasm (see CONTRAINDICATIONS), syndrome of abdominal pain, fever, chills, nausea and vomiting; acute renal failure in patients with pre-existing significantly impaired renal function, azotemia, cystitis, decreased creatinine clearance, hematuria, polyuria; dry eyes and mouth, gingival ulcers, rhinitis.

Precise Incidence Unknown (but less than 1%), Causal Relationship Unknown: Dream abnormalities, hallucinations, paresthesias, pseudotumor cerebri; photoallergic skin reactions, toxic epidermal necrolysis; cataracts, conjunctivitis, diplopia, optic neuritis; bleeding episodes (e.g., epistaxis, menorrhagia); acidosis, gynecomastia, hypoglycemic reactions; arrhythmias (sinus tachycardia, sinus bradycardia); angioedema, Henoch-Schönlein vasculitis, lupus erythematosus syndrome, serum sickness; renal papillary necrosis.

*Reactions occurring in 3% to 9% of adult patients treated with ibuprofen.

OVERDOSAGE: Patients with a history of ingestion of greater than 100 mg/kg should have induced emesis or gastric lavage. Multiple dose oral administration of activated charcoal may be useful. Supportive therapy may include oxygen, respiratory support, and parenteral fluids. Because the drug is acidic and excreted in the urine, administration of sodium bicarbonate and induction of diuresis may be beneficial.

DOSAGE AND ADMINISTRATION: Fever: 5 mg/kg if baseline temperature is 102.5°F or below or 10 mg/kg if baseline temperature is greater than 102.5°F, every 6-8 hours (children), 400 mg every 4-6 hours (adults).

Mild to moderate pain in adults: 400 mg every 4 to 6 hours.
Juvenile Arthritis: 30-40 mg/kg day in 3 or 4 divided doses.
RA and OA: 1200-3200 mg per day in 3 or 4 divided doses.
Dysmenorrhea: 400 mg every 4 hours.

HOW SUPPLIED: 4 and 16 oz. bottles

Caution: Federal law prohibits dispensing without prescription.

References:
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2. Independent Clinical Study: Reduction of Fever in Children, Multiple Dose. Data on file, Medical Department, Whitehall Laboratories.
3. Independent Clinical Study: Reduction of Fever in Children, Single Dose. Data on file, Medical Department, Whitehall Laboratories.

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Counting Words: Two initials are considered one word, each abbreviation is considered one word, and figures consisting of a dollar sign and five numerals or less are considered one word. Cities and states consisting of two words or more are counted as one word: i.e., "New York" and "Salt Lake City." Zip code is considered one word and must appear in all ads. Telephone number with area code is considered one word. When box numbers are used for replies, the words "Box ______, c/o AJDC" are to be counted as three words.

Classified Display	1 Time	3 Times
Full page	$1,155	$1,005
Two-thirds page	985	856
One-half page	809	704
One-third page	638	554
One-sixth page	295	257
Column inch	80	65

Minimum display ad: one column inch
12-time and 24-time rates available on request.

Display Production Charge: The publication will pub-set advertisements upon request. The typesetting fee is 10% of the one-time ad cost shown above. Special requests will be billed to the advertiser and/or agency at the then prevailing rates.

Box Service

Available for all ads. The cost is $15.00 for the first issue only. Responses to your ad will be consolidated in our office and promptly mailed directly to you.

Closing Date

The 25th of the second month prior to issue date. Example: The November issue closes September 25th. No ads can be cancelled after the closing date.

Send all copy, correspondence, production materials and payments to:

AMERICAN JOURNAL OF DISEASES OF CHILDREN
AJDC
Classified Department
P.O. Box 1510, Clearwater, Florida 34617

For assistance with your ad schedule call toll free:
800-237-9851 ☐ 813-443-7666

Professional Opportunities

SUFFOLK COUNTY NEW YORK — Seeking general pediatrician BE/BC part-time and vacation coverage to start, with possibility of full-time partnership. Call: (516) 589-6727.

PEDIATRICIAN PRACTICE OPPORTUNITY in beautiful Finger Lakes Area of Upstate New York. Income guarantee $75,000, malpractice, moving expenses paid, etc. Good coverage system, quality life environment, low crime rate. Proximal to larger educational and cultural centers of Syracuse, Rochester and Ithaca. Affiliated with modern, progressive hospital. CVs to: Henry Romano, MD, 187 Genesee Street, Auburn, NY 13021. For more information, call: Pat Nervina, Auburn Memorial Hospital, (315) 255-7224.

BC/BE PEDIATRICIAN to join two BC private practice pediatricians in upstate New York, Thousand Islands region. Affiliation leading to partnership. Level II NICU, cystic fibrosis center. Stimulating practice with an on-call arrangement with other pediatricians, excellent recreational facilities and schools in a thriving small city with many cultural advantages. A good place to raise children, too. Contact: R.G. Perciaccante, MD, 199 Pratt Street, Watertown, NY 13601.

NEONATOLOGIST to join five-member BC/BE group in a Level III perinatal center with academic affiliation. For further information, contact: B.T. Bloom, MD, 550 North Hillside, Wichita, KS 67214. (316) 688-2360.

THE DEPARTMENT OF PEDIATRICS, William Beaumont Hospital is seeking a second pediatric cardiologist to expand our Division of Pediatric Cardiology. William Beaumont Hospital is a 934-bed general hospital with 20 residency programs and a fully accredited training program in pediatrics. The Department of Pediatrics has 23 full-time, 12 part-time and a number of geographic full-time faculty. The inpatient service includes a 52-bed general pediatric ward, a 4-bed PICU (to increase to 6 beds by the summer) and a 30-bed NICU. We are anxious to recruit an individual who is interested in clinical care and teaching but who also has a definite interest in scholarly activity. Contact: M. Jeffrey Maisels, MD, Chairman, Department of Pediatrics, William Beaumont Hospital, 3601 West 13 Mile Road, Royal Oak, MI 48073-6769. (313) 551-0412.

LARGE MULTI-SPECIALTY GROUP in northern Virginia area needs bilingual pediatrician to replace retiring physician of 40 years. Send CV to: Medical Director, Falls Church Medical Center, 6060 Arlington Boulevard, Falls Church, VA 22044.

UPSTATE NEW YORK—BC/BE pediatrician to join well established pediatric group. Early partnership. Nice, safe community. Call or CV to: Felipe Canizares, MD, 421 Main Street, Oneida, NY 13421. (315) 363-2350.

EXCEPTIONAL PEDIATRIC PRACTICE opportunity available for a BC/BE pediatrician in a busy midwest multi-specialty clinic. Department currently consists of five pediatricians including services in general pediatrics, pediatric hematology/oncology and neonatolgy. Clinic is attached to a 206-bed hospital with a newly remodeled pediatric ward. It is located in a medically oriented community of 145,000 with excellent schools, two state universities and a private liberal arts college. A very low crime rate. Minnesota's lakes country just a half-hour drive away, thus outdoor activities abound. Excellent fringe benefits and a very competitive starting salary. Please contact: Dakota Clinic, Ltd., Recruiting Division, 1702 South University Drive, Fargo, ND 58103. (701) 280-8520.

Professional Opportunities

OBERLIN, OHIO — Multi-specialty group seeks BC/BE pediatricians to serve growing patient load. Northern Ohio college town serving drawing area of 275,000. Salary, liberal benefits first year with full shareholder status available thereafter. Send CV to: Dr. VanDyke, 224 West Lorain, Oberlin, OH 44074.

THIRD PEDIATRICIAN—BRAINERD, MINNESOTA: Join two pediatricians of 22 multi-specialty clinic. No set-up cost. Two hours from Minneapolis. Beautiful lakes and trees; ideal for families. Call collect/write: Curt Nielsen, (218) 828-7105 or (218) 829-4901; Brainerd Medical Center, P.O. Box 524, Brainerd, MN 56401.

FOUR CONGENIAL PEDIATRICIANS seek fifth pediatrician for rapidly expanding practice. This practice is located in an affluent growing community in northern California within a two-hour access to San Francisco and Lake Tahoe. Guaranteed salary for two years with partnership options at the end of the two-year period. Write or call: P.O. Box 787, Lodi, CA 95240. (209) 369-7493.

PHILADELPHIA AREA: Three pediatricians seeking BE/BC fourth in growing suburban community. One office practice, minutes from hospital. Full partnership opportunity after two years. Convenient access to Philadelphia, recreational opportunities in nearby Pocono Mountains and/or New Jersey Beaches. Send CV to: Stephen R. Gershenson, MD, 587 Bethlehem Pike, Montgomeryville, PA 18936.

PEDIATRICIAN

Children's Hospital of New Orleans is seeking board-certified or board-eligible pediatricians to provide part-time or full-time ambulatory services.

Responsibilities, based on individual preference, may include emergency room, outpatient services, child sexual abuse program, and transport or house coverage. Physicians are offered scheduled hours with no call responsibilities. Our 153-bed hospital, Louisiana's only full service pediatric facility, is affiliated with Tulane and Louisiana State University Schools of Medicine. All positions include medical student and/or resident teaching. Our staff of physicians and health professionals provides multi-disciplinary care to patients from Louisiana and the Gulf South.

New Orleans offers a warm climate, a variety of entertainment and leisure activities, and the country's best food and music. Louisiana license or qualification for licensure required.

For consideration, send CV to:

Alan Robson, MD, Medical Director

CHILDREN'S HOSPITAL
200 Henry Clay Avenue
New Orleans, LA 70118

PEDIATRICIAN

Immediate opportunity to associate with five pediatricians in a 70-doctor multi-specialty group. Drawing area of 400,000. Modern hospital within five minutes of clinic. Stimulating Big-10 university community of 110,000 with superb cultural advantages. Ideal for families. Medical school teaching affiliation if desired. Excellent initial guarantee and fringes with early associate status, subsequent income based exclusively on productivity. Send CV to:

RONALD H. DEERING, MD
Christie Clinic Association
101 West University
Champaign, IL 61820

Professional Opportunities

PEDIATRICIAN: Lovely agricultural, family oriented community located in western Nebraska (3 hours from Denver and Rocky Mountain snow activities) is seeking a fourth pediatrician. Choose from partnership, solo or salaried positions. Practice at the 270-bed regional referral center. Recieve a first year's income of $80,000 plus an attractive benefits package. This area has outstanding recreational activities and highly rated shcools. Call Lori at (800) 328-3666, or send CV to: Physician Source, 95 Cedar Lane, Englewood, NJ 07631.

PHILADELPHIA — Children's Hospital of Philadelphia seeks BC/BE pediatricians for its general pediatric practices. Exciting opportunity to practice in an academic setting. Responsibilities include ambulatory patient care and clinical teaching (affiliated with UPenn Medical School). Opportunities for clinical research and in-patient supervision. Competitive salary and excellent fringe benefits. Send CV to: Frances M. Gill, MD, Suite 2013, General Pediatrics, 1 Children's Plaza, Philadelphia, PA 19104. Children's Hospital of Philadelphia is an equal opportunity/affirmative action employer.

ALL PEDIATRIC SPECIALTIES — NATIONWIDE. Group/solo. Dr. Len Goodman, 5600 Executive Center Drive, #102, Charlotte, NC 28212. (704) 536-2527.

PEDIATRIC INTENSIVIST, cardiologist, pulmonologist — Join a team of nationally reowned physicians in the care of critically ill children in New Orleans! The practice is supported by a progressive 450-bed regional referral center with a drawing area in excess of 500,000. This team of pediatricians and pediatric subspecialists is building a premiere Pediatric Care Center which already includes a fully staffed PICU, pulmonary laboratory, cath laboratory, neurosurgery, and cardiovascular surgery. We seek a pediatric physician trained in either critical care, cardiology, or pulmonology who enjoys challenges and is committed to excellence in children's medicine. Excellent compensation and benefits are offered. Reply: Box #120, c/o AJDC.

Pediatric Subspecialists

Cardiology
Pulmonology
Hematology/Oncology
Neurology
Surgery
Neonatology

The University of South Dakota School of Medicine currently has openings for BE/BC pediatric subspecialties.

These are full-time academic positions ideally suited for the clinician scholar who wishes to develop and guide a program which will have a significant impact on the health care of children. Although our program is heavily slanted toward medical student education and patient care, the department encourages and provides ample resources for clinical and laboratory research.

Sioux Falls, included in David Frankes' book, America's Fifty Safest Cities, has a strong economic base, growing population and a progressive educational system. South Dakota's four season climate welcomes endless recreational activities year-round.

Competitive financial packages offered. EOE/AAE.

Send CV or call:
Carl Hinson • (800) 468-3333

USD School of Medicine
1100 South Euclid, P.O. Box 5039
Sioux Falls, SD 57117

Professional Opportunities

PEDIATRICIAN — Greene Clinic, a prestigious well-established clinic, wishes to add another pediatrician to its staff. The offices are in a new, $5.5 million, state-of-the-art facility, located in a university town outside a major metropolitan area. There is excellent call coverage with the other pediatricians in the group. A superior salary/compensation package is offered. It interested, please call Kevin McGrane at (800) 776-5776 to explore this opportunity further.

PEDIATRICIAN

Combine private practice efficiency and compensation with the rewards of community-oriented practice. Enjoy working with a practitioner-centered management team. Nearly rural living twenty minutes from metropolitan area allows the perfect reconciliation between love of family and passion for medicine.

Guaranteed salary, excellent benefit package. Flexible working schedule. Computerized office. Stimulating patient mix, friendly area. Health education, social work and mid-level support. Excellent local hospital referral centers nearby. Medical school affiliation and faculty appointment possible. Exciting educational opportunities at local college. Affordable housing, excellent schools. Varied recreational opportunities.

We've got it all!

Send CV to: James Goetz, MD
Medical Director

Oak Orchard
Community Health Center
80 West Avenue, Brockport, NY 14420

PROVIDENCE, RHODE ISLAND: Pediatrician to join seven others in well-run network of community health centers, serving multi-ethnic population. Involvement in Brown University's Medical School teaching program encouraged. Start any time between now and September. Call/write: Stanley Block, MD, Providence Ambulatory Health Care Foundation, 469 Angell Street, Providence, RI 02906. (401) 861-6300. An AA/EEE.

ADIRONDACK FOOTHILLS opportunity! Modern 124-bed hospital in upstate New York is offering a generous financial package for BC/BE pediatrician interested in establishing a private practice with excellent coverage arrangements. Guaranteed income, start-up funds, malpractice insurance, cash-flow assistance. Located in a family-oriented community with year-round recreation, excellent schools, and beautiful surroundings. Contact: Lyn I. Kucij, Director of Marketing and Development, Nathan Littauer Hospital, 99 East State Street, Gloversville, NY 12078. (518) 773-5504. Please call collect.

PEDIATRICIAN BC/BE: Seeking pediatrician for rapidly expanding practice in the Fox Valley of Illinois. Generous salary and amenities leading to partnership. Please send CV to: Pediatrics Associates, 1001 East Main, St. Charles, IL 60174; or call: (708) 584-7875.

NORTHWESTERN PENNSYLVANIA — BC pediatrician seeks second pediatrician (BC/BE) to be on team of well-established, quality care multi-specialty group of eighteen physicians in town of 15,000. Exceptional hospital with 12-bed pediatric unit and Level I Nursery serving 600 deliveries a year. Excellent living and working environment. Attractive salary and benefits. Send CV: Box #121, c/o AJDC.

IDAHO — Multi-specialty group of 27 physicians needs fourth pediatrician. Guaranteed salary plus bonus first year. Full stockholder status thereafter. Many fringe benefits and excellent outdoor recreational activities in agricultural area twenty miles from state capital. Office adjacent to 165-bed hospital with Level II Nursery. Contact: Mike Crane, 215 East Hawaii Avenue, Nampa, ID 83686. (208) 467-1121.

PLEASE NOTE — Address replies to box number ads as follows: Box number, ______, c/o AJDC, P.O. Box 1510, Clearwater, FL 34617.

Professional Opportunities

THE OHIO STATE UNIVERSITY Department of Pediatrics is seeking a board-certified/board-eligible pediatrician who has completed a fellowship in pulmonary medicine. Responsibilities include patient care, teaching and research in an academically oriented Children's Hospital. Competitive salary and benefits. Applicants should send curriculum vitae to: Karen McCoy, MD, Chairman, Pulmonary Search Committee, Children's Hospital, Inc., 700 Children's Drive, Columbus, OH 43205. The Ohio State University is an affirmative action/equal opportunity employer.

DELAWARE — General Pediatrician: The Nemours Foundation will develop several new general pediatric clinics in southern Delaware. These privately funded and administered clinics will offer a unique opportunity to serve a growing pediatric population in a coordinated statewide health care system. They will be located in underserved semi-rural areas and will consist of a general pediatrician and a pediatric nurse practitioner working together as a team in a modern computerized office setting. Tertiary care will be provided by the Alfred I. duPont Institute in Wilmington, Delaware. These clinics will be minutes from the Atlantic beaches and the Chesapeake Bay. The major metropolitan areas of Washington, Baltimore, Philadelphia and Wilmington will be within a two hour drive. If you have a desire to serve children in genuine need of good medical care, reply to the address below. Salary and fringes are distinctly above average. Reply to: The Alfred I. duPont Institute, Thomas P. Ferry, Administrator, P.O. Box 269, Wilmington, DE 19899. Telephone: (302) 651-4000.

Faculty Positions

SOUTHEAST USA — academic pediatrician: Teach medical students and family practice residents. Direct patient care and clinical research interests required. Alabama state medical license required. Should be board-eligible or board-certified. The University of Alabama is an equal opportunity affirmative action employer. Send inquiries with CV to: David C. Hefelfinger, MD, Department of Pediatrics, 700 University Boulevard East, Tuscaloosa, AL 35401. (205) 348-1304.

WYOMING — University of Wyoming Family Practice Residency-Casper is seeking an experienced, clinically oriented, board-certified pediatrician to be the pediatric coordinator of an 8-8-8 family practice residency program. Level II Nursery skills are a must. 60% teaching, 20% direct patient care, 20% research. This is a tenure track position. University approval will be required prior to filling this position. Come join us in beautiful Wyoming! Contact: Dr. David Driggers, Director, University of Wyoming Family Practice Residency, 1522 East "A" Street, Casper, WY 82601. (307) 266-3076. The University of Wyoming is an affirmative action/EOE.

JUNIOR FACULTY POSITION in the Division of General/Ambulatory Pediatrics is available at Texas Tech University Health Sciences Center, School of Medicine, Lubbock, Texas. Applicant must be board-eligible/-certified. Responsibilities include teaching, patient care and clinical research. Tenure track appointment available to qualified candidates. Call or submit CV to: V.J. Gururaj, MD, Professor, Director Division General/Ambulatory Pediatrics, Texas Tech University Health Sciences Center, School of Medicine, Department of Pediatrics, Lubbock, TX 79430. (806) 743-2266.

AMBULATORY PEDIATRICS Non specified — The Department of Pediatrics, University of Illinois College of Medicine at Rockford seeks a BC/BE pediatrician for an academic position in an ambulatory setting. The Community Health Center program is a longitudinal, comprehensive experience in primary care medicine. Each center is staffed by full-time faculty. Responsibilities include supervision of medical students in an ambulatory setting, direct patient care, quality assurance activities and clinical research. For earliest consideration please reply by: May 1, 1991. Reply with CV to: D.H. Wortmann, MD, Chairman, Department of Pediatrics, UICOM-R, 1400 Charles Street, Rockford, IL 61104. UICOM-R is an equal opportunity/affirmative action employer.

Fellowship
Child Abuse and Neglect Prevention Program
Medical College of Ohio

The Department of Pediatrics at the Medical College of Ohio in Toledo is seeking a BC/BE pediatrician for a two-year fellowship in the Child and Family Assessment Unit.

Applicant must be interested in the developmental and psychosocial aspects of pediatrics care as they relate to child abuse and neglect. Familiarity with the use of the colposcope desirable, but not essential. Ability to function in a multidisciplinary team setting necessary. Salary is $30,000 a year.

Inquiries should be directed to Brenda Ballmer, Department of Pediatrics, Medical College of Ohio, P.O. Box 10008, Toledo, Ohio 43699-0008, (419) 381-4485.

The Medical College of Ohio is an affirmative action/equal opportunity employer.

Directors Wanted

NEONATAL CO-DIRECTOR sought: BC/BE neonatologist for fee-for-service private practice in Level II, 18-bed nursery with 1,800 plus deliveries. Clinical, administrative and minimal teaching responsibilities (medical school and family practice residency). 150-bed, referral hospital located in Illinois university city. Great educational and recreational opportunities. Call Georgetta: (800) 328-3666.

Position Available

PEDIATRICIANS NEEDED: BE/BC full-time, needed to join Carle Clinic — Danville, Illinois; a 40,000+ rural, industrial community on the scenic Illinois/Indiana border, draws patients from both states. This 15 physician group is part of a 210 physician, multi-specialty, group practice in central Illinois; liberal fringe benefits including liability coverage, and competitive salary leading to equal ownership. Write, including CV to: Robert C. Parker, Jr., MD, Assistant to the Chief Executive Officer, Carle Clinic Association, 602 West University, Urbana, IL 61801. Or call collect at (217) 337-3417, FAX (217) 337-3163.

FLORIDA — Energetic, BC/BE pediatrician wanted to join large, nationally respected pediatric practice in Broward County, Florida, part-/full-time. Reply to: Peter Shulman, MD, Pediatric Associates, PA, 350 NW 70th Avenue, Suite 350A, Plantation, FL 33317. (305) 581-4400.

Practices Available

TEXAS—Eighteen-year-old, busy, solo pediatrics practice available. Three minutes outside Dallas, family oriented community, easily accessible to medical centers. Call: Dr. Gray, (214) 296-9930.

SACRAMENTO, CALIFORNIA: Busy, well-established solo general pediatrics practice for sale, owner retiring. Modern office near 250-bed community hospital with Levell III Nursery and neonatologist attented NICU. Two tertiary centers and full subspecialty consultation services nearby. Excellent leisure-time coverage available. Annual gross income $300K. 100 miles equidistant from coast and Sierra Nevada Mountains. Good schools and family oriented and recreational facilities. Must be BE/BC to apply. Terms negotiable. Will stay to introduce. Send CV to: Physician Relations Coordinator, Mercy San Juan Hospital, 6501 Coyle Avenue, Carmichael, CA 95608.

SOUTH CAROLINA — Growing pediatric practice in growth area of state. Low overhead with physician netting about $90,000. Close to dynamic Charleston. Contact: Gary Schaub, P.O. Box 69155, Portland, OR 97201. (503) 223-4357.

PLEASE NOTE—Address replies to box number ads as follows: Box number, ______, c/o AJDC, P.O. Box 1510, Clearwater, FL 34617.

We Target The Physician You Want!

The *American Journal of Diseases of Children's* classified recruitment advertising section is seen precisely by the physician you need – pediatricians and pediatric subspecialties. A total targeted physician audience of over 40,000.

Find the physician you need now. Send us your advertising order today. Just complete the coupon below and attach your typewritten copy. The next available issue is July which closes Monday, May 27th.

The classified rate is $1.85 per word for one issue. For three issues or more, the rate is $1.70 per word per issue. Minimum classified ad is 20 words.

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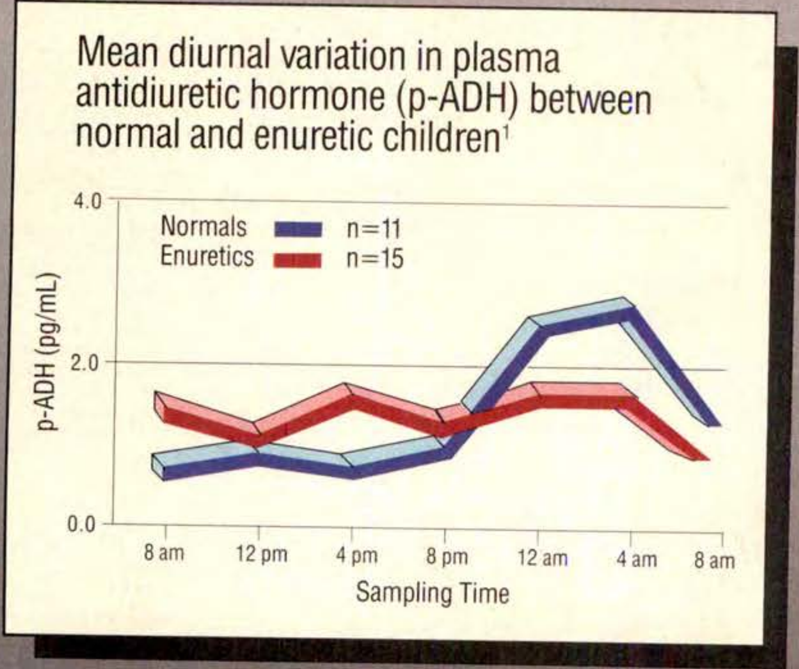
Authorized Signature __________

Send all copy and payments to:

AMERICAN JOURNAL OF DISEASES OF CHILDREN
AJDC

Classified Department
P.O. Box 1510, Clearwater, Florida 34617
National (800) 237-9851 ☐ Local (813) 443-7666

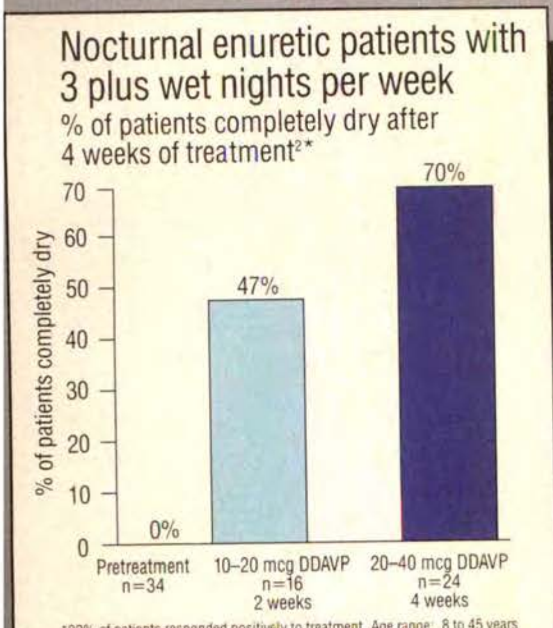
Landmark study concludes: Enuretic children may lack diurnal rhythm of ADH common in non-enuretic children[1]



Mean diurnal variation in plasma antidiuretic hormone (p-ADH) between normal and enuretic children[1]

The ADH Deficit

The first physiologic treatment for nocturnal enuresis



*82% of patients responded positively to treatment. Age range: 8 to 45 years

- DDAVP Nasal Spray, a synthetic analog of naturally occurring ADH, provides physiologic control of nighttime urine production in children 6 years of age or older[1-4]
- Clinically proven in all degrees of primary nocturnal enuresis, even in many patients resistant to imipramine and alarms[3]
- Easy to use — metered-dose nasal spray administered at bedtime
- Outstanding safety record in pediatric and adult patients[5]

DDAVP® Nasal Spray

(desmopressin acetate) 5mL

Safely Corrects the ADH Deficit

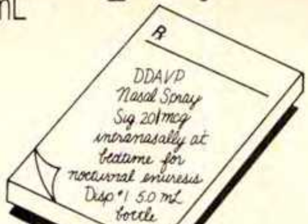
Please see next page for brief summary of prescribing information.

For more information
call 1-800-344-2525 ext. 6

DDAVP® Nasal Spray

(desmopressin acetate) 5mL

Safely Corrects the ADH Deficit



CONTRAINDICATION: Known hypersensitivity to DDAVP

WARNINGS: 1. For intranasal use only. 2. In very young and elderly patients in particular, fluid intake should be adjusted in order to decrease the potential occurrence of water intoxication and hyponatremia.

PRECAUTIONS:

General: DDAVP at high dosage has infrequently produced a slight elevation of blood pressure, which disappeared with a reduction in dosage. The drug should be used with caution in patients with coronary artery insufficiency and/or hypertensive cardiovascular disease because of possible rise in blood pressure.

Primary Nocturnal Enuresis: If changes in the nasal mucosa have occurred, unreliable absorption may result. DDAVP intranasal solution should be discontinued until the nasal problems resolve.

Information for Patients: Patients should be informed that the bottle accurately delivers 50 doses of 10 mcg each. Any solution remaining after 50 doses should be discarded since the amount delivered thereafter may be substantially less than 10 mcg of drug. No attempt should be made to transfer remaining solution to another bottle. Patients should be instructed to read accompanying directions on use of the spray pump carefully before use.

Laboratory Tests: For the healthy patient with primary nocturnal enuresis, serum electrolytes should be checked at least once if therapy is continued beyond 7 days.

DRUG INTERACTIONS: Although the pressor activity of DDAVP is very low compared to the antidiuretic activity, use of large doses of DDAVP with other pressor agents should only be done with careful patient monitoring.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY: Teratology studies in rats have shown no abnormalities. No further information is available.

PREGNANCY – CATEGORY B: Reproduction studies performed in rats and rabbits with doses up to 12.5 times the human intranasal dose (i.e. about 125 times the total adult human dose given systemically) have revealed no evidence of harm to the fetus due to desmopressin acetate. There are several publications of management of diabetes insipidus in pregnant women with no harm to the fetus reported; however, no controlled studies in pregnant women have been carried out. Published reports stress that, as opposed to preparations containing the natural hormones, DDAVP (desmopressin acetate) in antidiuretic doses has no uterotonic action, but the physician will have to weigh possible therapeutic advantages against possible dangers in each individual case.

NURSING MOTHERS: There have been no controlled studies in nursing mothers. A single study in a postpartum woman demonstrated a marked change in plasma, but little if any change in assayable DDAVP in breast milk following an intranasal dose of 10 mcg.

PEDIATRIC USE: Primary Nocturnal Enuresis: DDAVP has been used in childhood nocturnal enuresis. Short-term (4-8 weeks) DDAVP administration has been shown to be safe and modestly effective in children aged 6 years or older with severe childhood nocturnal enuresis. Adequately controlled studies with intranasal DDAVP in primary nocturnal enuresis have not been conducted beyond 4-8 weeks. The dose should be individually adjusted to achieve the best results.

There are reports of an occasional change in response with time, usually greater than 6 months. Some patients may show a decreased responsiveness, others a shortened duration of effect. There is no evidence this effect is due to the development of binding antibodies but may be due to a local inactivation of the peptide.

ADVERSE REACTIONS: Infrequently, high dosages have produced transient headache and nausea. Nasal congestion, rhinitis and flushing have also been reported occasionally along with mild abdominal cramps. These symptoms disappeared with reduction in dosage. Nosebleed, sore throat, cough and upper respiratory infections have also been reported.

The following table lists the percent of patients having adverse experiences without regard to relationship to study drug from the pooled pivotal study data for nocturnal enuresis.

ADVERSE REACTION	**PLACEBO (N=59)** %	**DDAVP 20 mcg (N=60)** %	**DDAVP 40 mcg (N=61)** %
BODY AS A WHOLE			
Abdominal Pain	0	2	2
Asthenia	0	0	2
Chills	0	0	2
Headache	0	2	5
Throat Pain	2	0	0
NERVOUS SYSTEM			
Depression	2	0	0
Dizziness	0	0	3
RESPIRATORY SYSTEM			
Epistaxis	2	3	0
Nostril Pain	0	2	0
Respiratory Infection	2	0	0
Rhinitis	2	8	3
CARDIOVASCULAR SYSTEM			
Vasodilation	2	0	0
DIGESTIVE SYSTEM			
Gastrointestinal Disorder	0	2	0
Nausea	0	0	2
SKIN & APPENDAGES			
Leg Rash	2	0	0
Rash	2	0	0
SPECIAL SENSES			
Conjunctivitis	0	2	0
Edema Eyes	0	2	0
Lachrymation Disorder	0	0	2

OVERDOSAGE: See adverse reactions above. In case of overdosage, the dose should be reduced, frequency of administration decreased, or the drug withdrawn according to the severity of the condition. There is no known specific antidote for DDAVP.

An oral LD_{50} has not been established. An intravenous dose of 2 mg/kg in mice demonstrated no effect.

HOW SUPPLIED: A 5 mL bottle with spray pump delivering 50 doses of 10 mcg (NDC 0075-2450-02). Keep refrigerated at 36°-46°F (2°-8°C). When traveling, product will maintain stability for up to 3 weeks when stored at room temperature, 72°F (22°C).

See product circular for full prescribing information. Rev. 6/89

1. Rittig S, Knudsen UB, Nørgaard JP, et al: Abnormal diurnal rhythm of plasma vasopressin and urinary output in patients with enuresis. *Am J Physiol* 1989;25(4):F664-F671. 2. Rittig S, Knudsen UB, Sørensen S, et al: Long-term double-blind cross-over study of desmopressin intranasal spray in the management of nocturnal enuresis. In: Meadow SR, ed. *Desmopressin in Nocturnal Enuresis: Proceedings of an International Symposium.* England: Horus Medical Publications; 1988:43-55. 3. Dimson SB: DDAVP and urine osmolality in refractory enuresis. *Arch Dis Child* 1986;61:1104-1107. 4. Data on file, Rhône-Poulenc Rorer Pharmaceuticals Inc. 5. Richardson DW, Robinson AG: Diagnosis and treatment: Drugs five years later: Desmopressin. *Ann Intern Med* 1985;103:228-239.

Manufactured for
RHÔNE-POULENC RORER

RHÔNE-POULENC RORER PHARMACEUTICALS INC.
500 VIRGINIA DRIVE
FORT WASHINGTON, PA 19034
By Ferring Pharmaceuticals, Malmö, Sweden

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INDEX TO ADVERTISERS

Connaught Laboratories 484

Fisons Corporation 482

Lederle Laboratories 488A-B

McNeil Consumer Products Company 485-486, 496A-B

Mead Johnson Nutritional Division .... Cover 2, 535

Merck Sharp & Dohme
Division of Merck & Co., Inc. 497-498

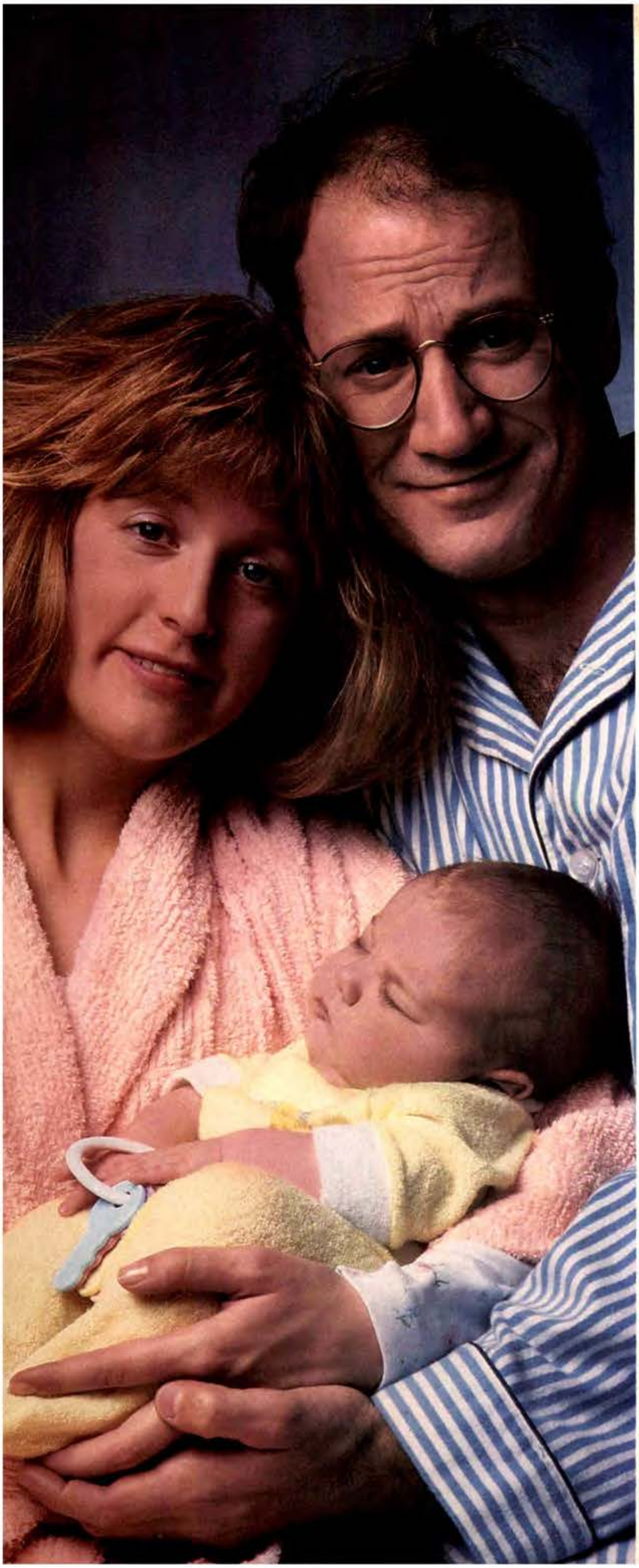
Partnership For A Drug-Free America 586

Reed & Carnrick .... Cover 3

Rorer Pharmaceuticals 586-588

Wyeth-Ayerst Laboratories .... 493-494, 533-534, 563-564, 581-582, Cover 4

While every precaution is taken to ensure accuracy, we cannot guarantee against the possibility of an occasional change or omission in the preparation of this index.



Family therapy for colic.

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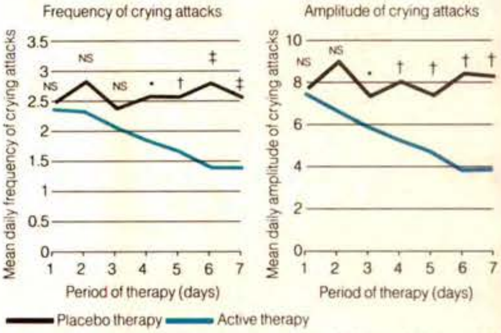

p values (active vs. placebo) NS = Not significant •$p < 0.05$ †$p < 0.02$ ‡$p < 0.01$

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[1] Kanwaljit SS, Jasbir KS. Simethicone in the management of infant colic. *Practitioner.* 1988;232:508.

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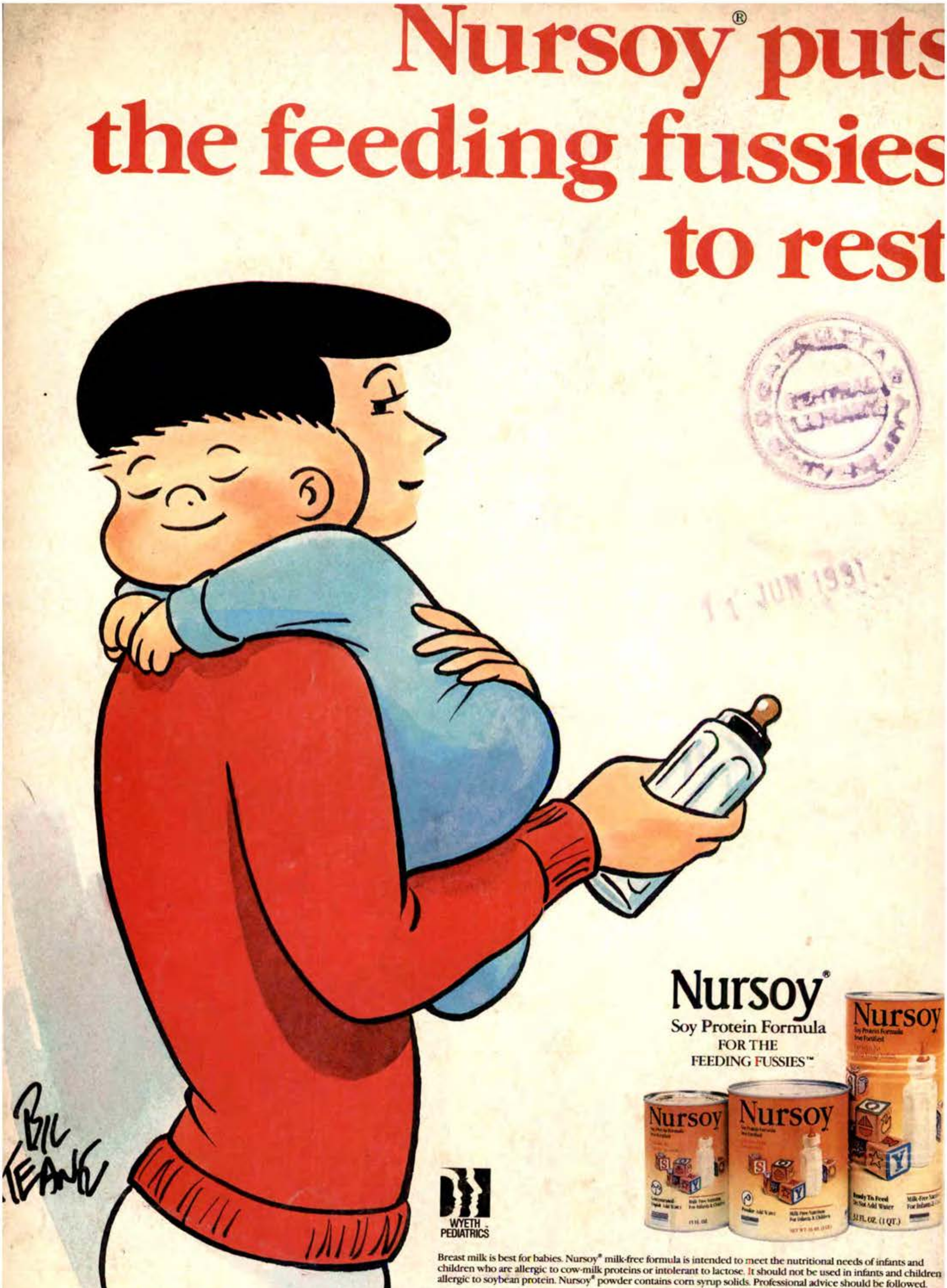

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72

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JUNE 1991

Detection of Alcoholism in Hospitalized Children and Their Families

A. K. Duggan, H. Adger, Jr, E. M. McDonald, E. J. Stokes, R. Moore

---

Dietary Calcium and Bone Mineral Status of Children and Adolescents

G. M. Chan

Influenza Type A and B Infections in Hospitalized Pediatric Patients: Who Should Be Immunized?

J. R. Serwint, R. M. Miller, B. M. Korsch

Pediatric Cardiac Rehabilitation

I. C. Balfour, A. M. Drimmer, S. Nouri,
D. G. Pennington, C. L. Hemkens, L. L. Harvey

Chief Resident Training: Developing Leadership Skills for Future Medical Leaders

R. A. Doughty, P. D. Williams, C. N. Seashore

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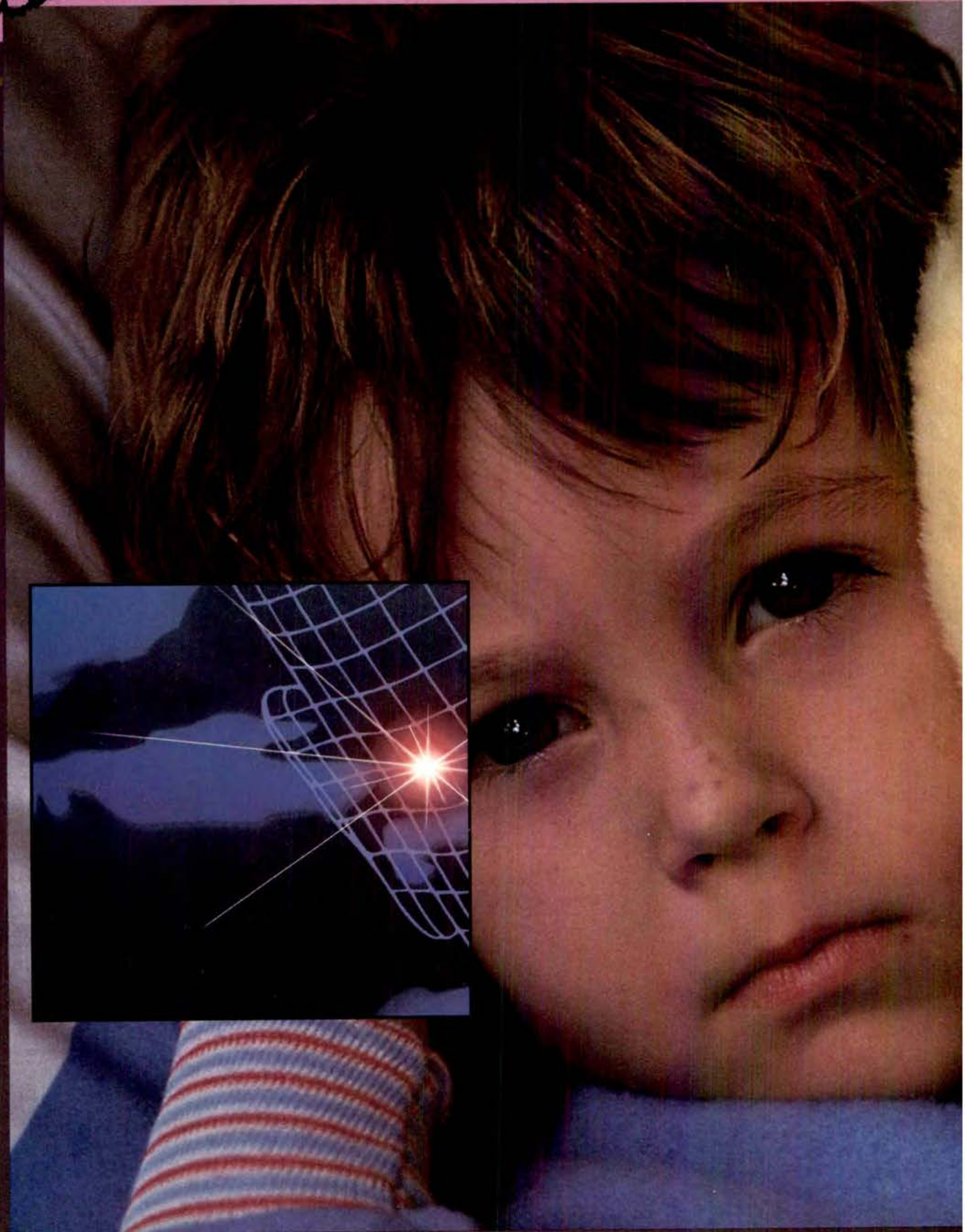

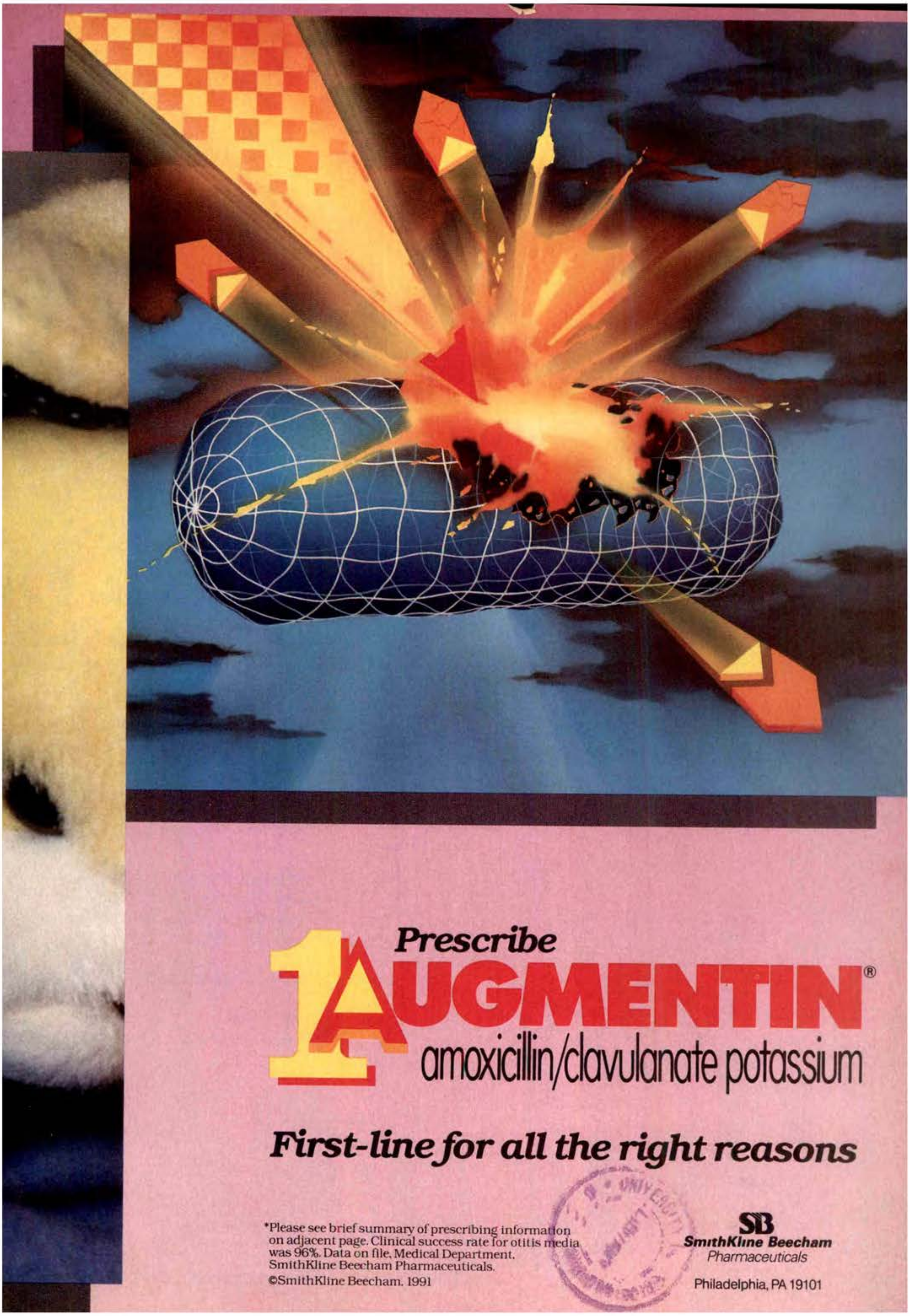

Prescribe

AUGMENTIN®

amoxicillin/clavulanate potassium

First-line for all the right reasons

*Please see brief summary of prescribing information on adjacent page. Clinical success rate for otitis media was 96%. Data on file, Medical Department, SmithKline Beecham Pharmaceuticals.

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Brief Summary of Prescribing Information

AUGMENTIN® amoxicillin/clavulanate potassium

Indications and Usage: *Augmentin* is indicated in the treatment of infections caused by susceptible strains of the designated organisms in the conditions listed below:

Lower Respiratory Infections caused by β-lactamase-producing strains of *Hemophilus influenzae* and *Branhamella catarrhalis*.

Otitis Media caused by β-lactamase-producing strains of *Hemophilus influenzae* and *Branhamella catarrhalis*.

Sinusitis caused by β-lactamase-producing strains of *Hemophilus influenzae* and *Branhamella catarrhalis*.

Skin and Skin Structure Infections caused by β-lactamase-producing strains of *Staphylococcus aureus*, *E. coli*, and *Klebsiella* spp.

Urinary Tract Infections caused by β-lactamase-producing strains of *E. coli*, *Klebsiella* spp. and *Enterobacter* spp.

While *Augmentin* is indicated only for the conditions listed above, infections caused by ampicillin-susceptible organisms are also amenable to *Augmentin* treatment due to its amoxicillin content. Therefore, mixed infections caused by ampicillin susceptible organisms and β-lactamase-producing organisms susceptible to *Augmentin* should not require the addition of another antibiotic.

Bacteriological studies, to determine the causative organisms and their susceptibility to *Augmentin*, should be performed together with any indicated surgical procedures.

Therapy may be instituted prior to obtaining the results from bacteriological and susceptibility studies to determine the causative organisms and their susceptibility to *Augmentin* when there is reason to believe the infection may involve any of the β-lactamase-producing organisms listed above. Once the results are known, therapy should be adjusted, if appropriate.

Contraindications: A history of allergic reactions to any penicillin is a contraindication.

WARNINGS: SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTOID) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY. ALTHOUGH ANAPHYLAXIS IS MORE FREQUENT FOLLOWING PARENTERAL THERAPY, IT HAS OCCURRED IN PATIENTS ON ORAL PENICILLINS. THESE REACTIONS ARE MORE LIKELY TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY AND/OR A HISTORY OF SENSITIVITY TO MULTIPLE ALLERGENS. THERE HAVE BEEN REPORTS OF INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHEN TREATED WITH CEPHALOSPORINS. BEFORE INITIATING THERAPY WITH ANY PENICILLIN, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS, OR OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, *AUGMENTIN* SHOULD BE DISCONTINUED AND THE APPROPRIATE THERAPY INSTITUTED. **SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN, INTRAVENOUS STEROIDS, AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.**

Precautions: General: While *Augmentin* possesses the characteristic low toxicity of the penicillin group of antibiotics, periodic assessment of organ system functions, including renal, hepatic and hematopoietic function, is advisable during prolonged therapy.

A high percentage of patients with mononucleosis who receive ampicillin develop a skin rash. Thus, ampicillin class antibiotics should not be administered to patients with mononucleosis.

The possibility of superinfections with mycotic or bacterial pathogens should be kept in mind during therapy. If superinfections occur (usually involving *Pseudomonas* or *Candida*), the drug should be discontinued and/or appropriate therapy instituted.

Drug Interactions: Probenecid decreases the renal tubular secretion of amoxicillin. Concurrent use with *Augmentin* may result in increased and prolonged blood levels of amoxicillin.

The concurrent administration of allopurinol and ampicillin increases substantially the incidence of rashes in patients receiving both drugs as compared to patients receiving ampicillin alone. It is not known whether this potentiation of ampicillin rashes is due to allopurinol or the hyperuricemia present in these patients. There are no data with *Augmentin* and allopurinol administered concurrently.

Augmentin should not be co-administered with Antabuse® (disulfiram).

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate carcinogenic or mutagenic potential.

Pregnancy (Category B): Reproduction studies have been performed in mice and rats at doses up to ten (10) times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to *Augmentin*. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery: Oral ampicillin class antibiotics are generally poorly absorbed during labor. Studies in guinea pigs have shown that intravenous administration of ampicillin decreased the uterine tone, frequency of contractions, height of contractions and duration of contractions. However, it is not known whether the use of *Augmentin* in humans during labor or delivery has immediate or delayed adverse effects on the fetus, prolongs the duration of labor or increases the likelihood that forceps delivery or other obstetrical intervention or resuscitation of the newborn will be necessary.

Nursing Mothers: Ampicillin class antibiotics are excreted in the milk; therefore, caution should be exercised when *Augmentin* is administered to a nursing woman.

Adverse Reactions: *Augmentin* is generally well tolerated. The majority of side effects observed in clinical trials were of a mild and transient nature and less than 3% of patients discontinued therapy because of drug-related side effects. The most frequently reported adverse effects were diarrhea/loose stools (9%), nausea (3%), skin rashes and urticaria (3%), vomiting (1%) and vaginitis (1%).

The overall incidence of side effects, and in particular diarrhea, increased with the higher recommended dose. Other less frequently reported reactions include: abdominal discomfort, flatulence and headache.

The following adverse reactions have been reported for ampicillin class antibiotics:

Gastrointestinal: Diarrhea, nausea, vomiting, indigestion, gastritis, stomatitis, glossitis, black "hairy" tongue, enterocolitis and pseudomembranous colitis.

Hypersensitivity reactions: Skin rashes, urticaria, angioedema, serum sickness-like reactions (urticaria or skin rash accompanied by arthritis/arthralgia, myalgia, and frequently fever), erythema multiforme (rarely Stevens-Johnson Syndrome), and an occasional case of exfoliative dermatitis have been reported. These reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids. Whenever such reactions occur the drug should be discontinued, unless the opinion of the physician dictates otherwise. Serious and occasional fatal hypersensitivity (anaphylactic) reactions can occur with oral penicillin (See Warnings).

Liver: A moderate rise in SGOT, SGPT, AST, and/or ALT has been noted in patients treated with ampicillin class antibiotics including *Augmentin*. The significance of these findings is unknown. As with some other penicillins and some cephalosporins, hepatic dysfunction has been reported rarely, with the predominant effects being cholestatic, hepatocellular, or mixed cholestatic-hepatocellular. Signs/symptoms may appear during or after therapy and they resolve completely over time.

Hemic and Lymphatic Systems: Anemia, thrombocytopenia, thrombocytopenic purpura, eosinophilia, leukopenia and agranulocytosis have been reported during therapy with penicillins. These reactions are usually reversible on discontinuation of therapy and are believed to be hypersensitivity phenomena. A slight thrombocytosis was noted in less than 1% of the patients treated with *Augmentin*.

Central Nervous System: Reversible hyperactivity, agitation, anxiety, insomnia, confusion, behavioral changes, and/or dizziness have been reported rarely.

Dosage: Adults: The usual adult dose is one *Augmentin* '250' tablet every eight hours. For more severe infections and infections of the respiratory tract, the dose should be one *Augmentin* '500' tablet every eight hours.

Since both the *Augmentin* '250' and '500' tablets contain the same amount of clavulanic acid (125 mg, as the potassium salt), two *Augmentin* '250' tablets are not equivalent to one *Augmentin* '500' tablet. Therefore, two *Augmentin* '250' tablets should not be substituted for one *Augmentin* '500' tablet for treatment of more severe infections.

Children: The usual dose is 20 mg/kg/day, based on amoxicillin component, in divided doses every eight hours. For otitis media, sinusitis and other more severe infections, the dose should be 40 mg/kg/day, based on the amoxicillin component, in divided doses every eight hours. Also available as *Augmentin* '125' and '250' chewable tablets.

Children weighing 40 kg and more should be dosed according to the adult recommendations.

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AMERICAN JOURNAL OF
DISEASES OF CHILDREN

AJDC

Vol 145 **No. 6** **JUNE 1991**

THE PEDIATRIC FORUM

Comments on Life After Residency 597
Robert L. Brent, MD, PhD, Philadelphia, Pa

How Much Iron Is Enough? 598
William B. Rogers, MD, Cuyahoga Falls, Ohio

In Reply 598
Laurence Finberg, MD, Brooklyn, NY

Acute Glossitis and Bacteremia Caused by *Streptococcus pneumoniae*: Case Report and Review 598
Jeffrey J. Stoddard, MD, Jayant K. Deshpande, MD, Baltimore, Md

Puncture Wound — Induced *Achromobacter xylosoxidans* Osteomyelitis of the Foot 599
David M. Hoddy, MD, St Louis, Mo, Leslie L. Barton, MD, Tucson, Ariz

Condylomata Acuminata: Still Usually a Sexually Transmitted Disease in Children 600
John M. Goldenring, MD, MPH, Redlands, Calif

In Reply 601
Alan S. Boyd, MD, Lubbock, Tex

Lead Poisoning in Children With Developmental Disabilities 602
Stephen B. Sulkes, MD, Rochester, NY,
Dennis W. O'Connor, MD, Bath, NY

Neurodevelopmental Outcome of Offspring of the Diabetic Mother: Need for Further Research 602
Esther Goldstein, PhD; Basil Porter, MBBCh;
Aharon Galil, MD, Beer Sheva, Israel

Albuterol Inhalations in Acute Chest Syndrome 603
Edward Handelsman, MD, New Hyde Park, NY,
Debra Voulalas, MD, Philadelphia, Pa

Penile Vasculitis With Impending Necrosis Treated With Prostaglandin E_1 Infusion 604
Anthony A. Horner, MD; Karen Dunn, MD;
E. Richard Stiehm, MD, Los Angeles, Calif

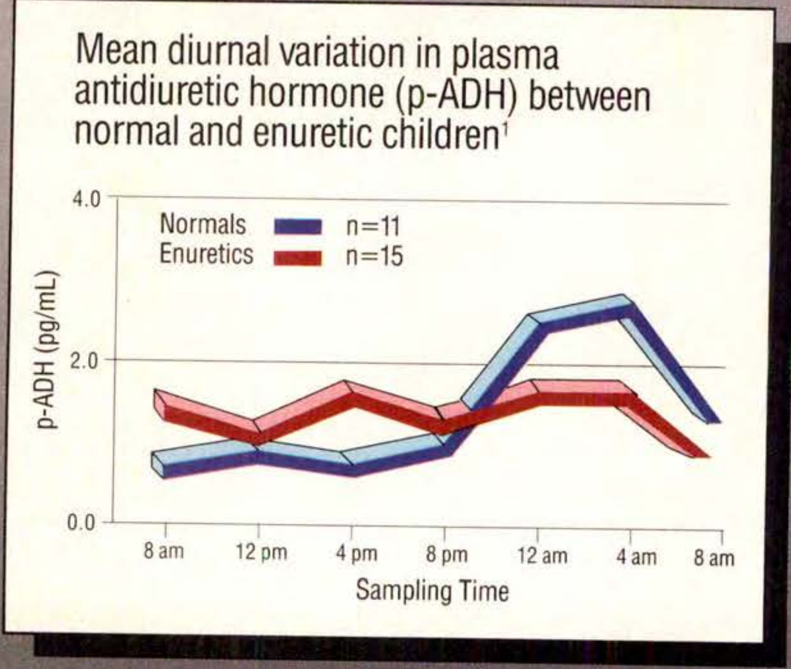
THE EDITORIAL BOARD SPEAKS

Losing Time 607
Albert W. Pruitt, MD, Augusta, Ga

Continued on page 595.

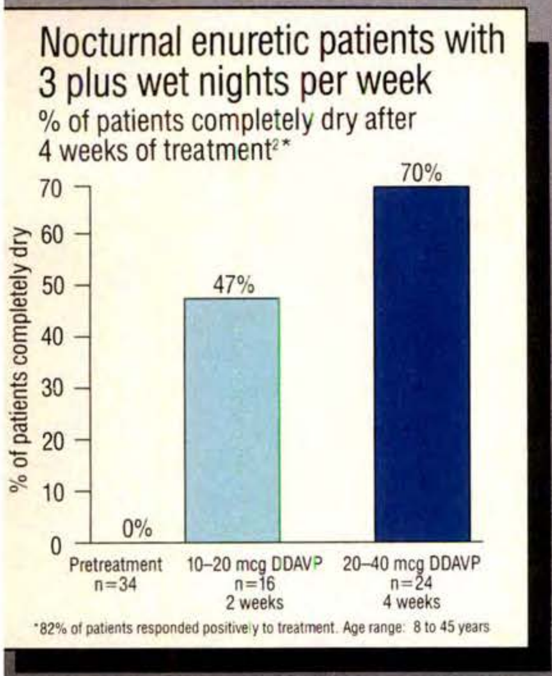
Landmark study concludes: Enuretic children may lack diurnal rhythm of ADH common in non-enuretic children[1]

Mean diurnal variation in plasma antidiuretic hormone (p-ADH) between normal and enuretic children[1]



The ADH Deficit

The first physiologic treatment for nocturnal enuresis



Nocturnal enuretic patients with 3 plus wet nights per week

% of patients completely dry after 4 weeks of treatment[2]*

*82% of patients responded positively to treatment. Age range: 8 to 45 years

- DDAVP Nasal Spray, a synthetic analog of naturally occurring ADH, provides physiologic control of nighttime urine production in children 6 years of age or older[1-4]
- Clinically proven in all degrees of primary nocturnal enuresis, even in many patients resistant to imipramine and alarms[3]
- Easy to use — metered-dose nasal spray administered at bedtime
- Outstanding safety record in pediatric and adult patients[5]

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desmopressin acetate) 5mL

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Please see next page for brief summary of prescribing information.

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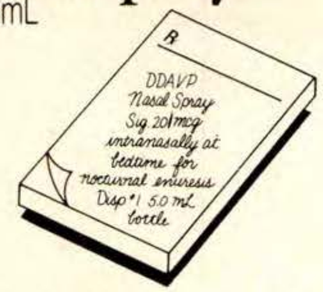

CONTRAINDICATION: Known hypersensitivity to DDAVP

WARNINGS: 1. For intranasal use only.
2. In very young and elderly patients in particular, fluid intake should be adjusted in order to decrease the potential occurrence of water intoxication and hyponatremia.

PRECAUTIONS:

General: DDAVP at high dosage has infrequently produced a slight elevation of blood pressure, which disappeared with a reduction in dosage. The drug should be used with caution in patients with coronary artery insufficiency and/or hypertensive cardiovascular disease because of possible rise in blood pressure.

Primary Nocturnal Enuresis: If changes in the nasal mucosa have occurred, unreliable absorption may result. DDAVP intranasal solution should be discontinued until the nasal problems resolve.

Information for Patients: Patients should be informed that the bottle accurately delivers 50 doses of 10 mcg each. Any solution remaining after 50 doses should be discarded since the amount delivered thereafter may be substantially less than 10 mcg of drug. No attempt should be made to transfer remaining solution to another bottle. Patients should be instructed to read accompanying directions on use of the spray pump carefully before use.

Laboratory Tests: For the healthy patient with primary nocturnal enuresis, serum electrolytes should be checked at least once if therapy is continued beyond 7 days.

DRUG INTERACTIONS: Although the pressor activity of DDAVP is very low compared to the antidiuretic activity, use of large doses of DDAVP with other pressor agents should only be done with careful patient monitoring.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY: Teratology studies in rats have shown no abnormalities. No further information is available.

PREGNANCY – CATEGORY B: Reproduction studies performed in rats and rabbits with doses up to 12.5 times the human intranasal dose (i.e. about 125 times the total adult human dose given systemically) have revealed no evidence of harm to the fetus due to desmopressin acetate. There are several publications of management of diabetes insipidus in pregnant women with no harm to the fetus reported; however, no controlled studies in pregnant women have been carried out. Published reports stress that, as opposed to preparations containing the natural hormones, DDAVP (desmopressin acetate) in antidiuretic doses has no uterotonic action, but the physician will have to weigh possible therapeutic advantages against possible dangers in each individual case.

NURSING MOTHERS: There have been no controlled studies in nursing mothers. A single study in a post-partum woman demonstrated a marked change in plasma, but little if any change in assayable DDAVP in breast milk following an intranasal dose of 10 mcg.

PEDIATRIC USE: Primary Nocturnal Enuresis: DDAVP has been used in childhood nocturnal enuresis. Short-term (4-8 weeks) DDAVP administration has been shown to be safe and modestly effective in children aged 6 years or older with severe childhood nocturnal enuresis. Adequately controlled studies with intranasal DDAVP in primary nocturnal enuresis have not been conducted beyond 4-8 weeks. The dose should be individually adjusted to achieve the best results.

There are reports of an occasional change in response with time, usually greater than 6 months. Some patients may show a decreased responsiveness, others a shortened duration of effect. There is no evidence this effect is due to the development of binding antibodies but may be due to a local inactivation of the peptide.

ADVERSE REACTIONS: Infrequently, high dosages have produced transient headache and nausea. Nasal congestion, rhinitis and flushing have also been reported occasionally along with mild abdominal cramps. These symptoms disappeared with reduction in dosage. Nosebleed, sore throat, cough and upper respiratory infections have also been reported.

The following table lists the percent of patients having adverse experiences without regard to relationship to study drug from the pooled pivotal study data for nocturnal enuresis.

ADVERSE REACTION	PLACEBO (N=59)	DDAVP 20 mcg (N=60)	DDAVP 40 mcg (N=61)
	%	%	%
BODY AS A WHOLE			
Abdominal Pain	0	2	2
Asthenia	0	0	2
Chills	0	0	2
Headache	0	2	5
Throat Pain	2	0	0
NERVOUS SYSTEM			
Depression	2	0	0
Dizziness	0	0	3
RESPIRATORY SYSTEM			
Epistaxis	2	3	0
Nostril Pain	0	2	0
Respiratory Infection	2	0	0
Rhinitis	2	8	3
CARDIOVASCULAR SYSTEM			
Vasodilation	2	0	0
DIGESTIVE SYSTEM			
Gastrointestinal Disorder	0	2	0
Nausea	0	0	2
SKIN & APPENDAGES			
Leg Rash	2	0	0
Rash	2	0	0
SPECIAL SENSES			
Conjunctivitis	0	2	0
Edema Eyes	0	2	0
Lachrymation Disorder	0	0	2

OVERDOSAGE: See adverse reactions above. In case of overdosage, the dose should be reduced, frequency of administration decreased, or the drug withdrawn according to the severity of the condition. There is no known specific antidote for DDAVP.

An oral LD_{50} has not been established. An intravenous dose of 2 mg/kg in mice demonstrated no effect.

HOW SUPPLIED: A 5 mL bottle with spray pump delivering 50 doses of 10 mcg (NDC 0075-2450-02). Keep refrigerated at 36°-46°F (2°-8°C). When traveling, product will maintain stability for up to 3 weeks when stored at room temperature, 72°F (22°C).

See product circular for full prescribing information. Rev. 6/89

1. Rittig S, Knudsen UB, Nørgaard JP, et al: Abnormal diurnal rhythm of plasma vasopressin and urinary output in patients with enuresis. *Am J Physiol* 1989;25(4):F664-F671. 2. Rittig S, Knudsen UB, Sørensen S, et al: Long-term double-blind cross-over study of desmopressin intranasal spray in the management of nocturnal enuresis. In: Meadow SR, ed. *Desmopressin in Nocturnal Enuresis: Proceedings of an International Symposium.* England: Horus Medical Publications; 1988:43-55. 3. Dimson SB: DDAVP and urine osmolality in refractory enuresis. *Arch Dis Child* 1986;61:1104-1107. 4. Data on file, Rhône-Poulenc Rorer Pharmaceuticals Inc. 5. Richardson DW, Robinson AG: Diagnosis and treatment: Drugs five years later: Desmopressin. *Ann Intern Med* 1985;103:228-239.

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Rorer Pharmaceuticals 592-594

SmithKline-Beecham Laboratories ..... Cover 2-590, Cover 3

Wyeth-Ayerst Laboratories 611-612, 635-636, 643-644
Cover 4

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AMERICAN JOURNAL OF DISEASES OF CHILDREN

EDITORIAL

Parental Alcoholism: A Neglected Pediatric Responsibility 609
Donald Ian Macdonald, MD, Bethesda, Md

ARTICLES

Detection of Alcoholism in Hospitalized Children and Their Families 613
Anne K. Duggan, ScD; Hoover Adger, Jr, MD, MPH; Eileen M. McDonald; Emma J. Stokes, PhD; Richard Moore, MD, MHS, Baltimore, Md

The Causes of Hospital-Treated Acute Lower Respiratory Tract Infection in Children 618
Hanna Nohynek, MD; Juhani Eskola, MD; Eija Laine, MD, Helsinki, Finland; Pekka Halonen, MD, Turku, Finland; Petri Ruutu, MD; Pekka Saikku, MD; Marjaana Kleemola, MD; Maija Leinonen, PhD, Helsinki, Finland

Influenza Type A and B Infections in Hospitalized Pediatric Patients: Who Should Be Immunized? 623
Janet R. Serwint, MD; Ross M. Miller, MD; Barbara M. Korsch, MD, Los Angeles, Calif

Pediatric Cardiac Rehabilitation 627
Ian C. Balfour, MBBS; Ami M. Drimmer, PhD; Soraya Nouri, MBBS; D. Glenn Pennington, MD; Carol L. Hemkens, RN; Linda L. Harvey, RN, St Louis, Mo

Dietary Calcium and Bone Mineral Status of Children and Adolescents 631
Gary M. Chan, MD, Salt Lake City, Utah

Percentile Curves for Various Hematologic Measurements at Birth in Arab Preterm Babies of Different Gestational Ages 645
Khalid N. Haque, FRCP, DCH, Hassan M. Bahakim, MD, Riyadh, Saudi Arabia

Meconium for Drug Testing 650
Edward C. Maynard, MD, Worcester, Mass; Louis P. Amoruso, PhD, Mansfield, Mass; William Oh, MD, Providence, RI

Guidelines for Safe Transportation of Children in Wheelchairs 653
Kathleen M. DiGaudio, RN, MSN, PNP, Michael E. Msall, MD, Buffalo, NY

Osteochondrodysplasia in Fryns Syndrome 656
Matthew M. Kershisnik, MD; Catherine M. Craven, MD; A. L. Jung, MD; John C. Carey, MD; A. S. Knisely, MD, Salt Lake City, Utah

Autosomal Recessive Lethal Infantile Cytochrome C Oxidase Deficiency 661
Gideon Eshel, MD; Eliezer Lahat, MD; Kalman Fried, MD, PhD; Josef Barr, MD, Tel Aviv, Israel; Varda Barash, MD; Alisa Gutman, MD, Jerusalem, Israel; Salvatore DiMauro, MD, New York, NY; Mordechei Aladjem, MD, Tel Aviv, Israel

***Escherichia coli* Bacteremia in Children: A Review of 91 Cases in 10 Years** 671
William A. Bonadio, MD; Douglas S. Smith, MD; Elisabeth Madagame, MD; Jane Machi, MD; Narendra Kini, MD, Milwaukee, Wis

Continued on page 596.

AMERICAN JOURNAL OF DISEASES OF CHILDREN

Factors Associated With Umbilical Catheter-Related Sepsis in Neonates 675
Susan Landers, MD; Alicia A. Moise, MD; J. Kennard Fraley, MPH; E. O'Brian Smith, PhD; Carol J. Baker, MD, Houston, Tex

A 50-Year Follow-up of Childhood Plumbism: Hypertension, Renal Function, and Hemoglobin Levels Among Survivors 681
Howard Hu, MD, MPH, ScD, Boston, Mass

Brain and Ocular Abnormalities in Infants With In Utero Exposure to Cocaine and Other Street Drugs 688
Rodrigo Dominguez, MD; Antonio Aguirre Vila-Coro, MD; John M. Slopis, MD; Timothy Bohan, MD, PhD, Houston, Tex

A Preliminary Report of Prenatal Cocaine Exposure and Respiratory Distress Syndrome in Premature Infants 696
Barry Zuckerman, MD; Edward C. Maynard, MD; Howard Cabral, MPH, Boston, Mass

EDUCATIONAL INTERVENTION

Chief Resident Training: Developing Leadership Skills for Future Medical Leaders 639
Robert A. Doughty, MD, PhD; Patricia D. Williams, MD; Charles N. Seashore, PhD, Wilmington, Del

SPORTS MEDICINE

Tracking of Elevated Blood Pressure Values in Adolescent Athletes at 1-Year Follow-up 665
Jeffrey L. Tanji, MD, Sacramento, Calif

SPECIAL FEATURES

Radiological Case of the Month 699
David Ponder, MD; Gary S. Marshall, MD; Gerard P. Rabalais, MD, Louisville, Ky; Beverly P. Wood, MD, Los Angeles, Calif

Picture of the Month 701
Merlin G. Butler, MD, PhD, Sarah Hassell, MD, Nashville, Tenn; Murray Feingold, MD, Walter W. Tunnessen, Jr, MD, Brighton, Mass

REGULAR DEPARTMENTS

Index to Advertisers 594

Classified Advertising 706

Instructions for Authors (See May 1991 issue, p 488.)

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PEDIATRIC FORUM

Comments on Life After Residency

Sir.—I read the editorial by Boyce[1] in the August 1990 issue of *AJDC* and believe it discusses a subject that should be of great interest to everyone. Dr Boyce is a thoughtful and kind individual who has given the reader his "highly personal" view on this subject. While personal views are sometimes insightful and creative, they may also fail to note that there may be extensive literature on the subject.

Twenty-five years ago, I began what has evolved into an annual lecture to freshmen medical students at Jefferson Medical College, Philadelphia, Pa, entitled "Medicine, An Excuse From Living."[2] It was published in 1978 and reprinted in 1990.[3] Before and since the 1978 publication, many articles have been published dealing with this subject. The publications are not all in agreement and they do not reflect the same level of scholarship or insight.

Dr Boyce discusses five criteria or assumptions that he believes "guide our collective approach" to setting priorities and making key decisions. Some might refer to these concepts as dogma or truisms: (1) "The development of meaningful personal relationships (such as one's marriage) can and often must be postponed until certain professional goals are attained." (2) "Medicine must be the physician's highest priority (with the corollary that the more time devoted to medicine, the greater the rewards)." (3) "The single objective in setting priorities is to establish a balance between work life and home life." (4) "In most issues of competing demands on time, efficiency is the solution." (5) "Lack of time with children can be balanced by spending 'quality time.'" Dr Boyce's comments about these criteria are sensitive and thoughtful, but they are of little assistance to the individual who wishes to prevent personal or professional tragedies. His approach is a positive one but he does not address the reasons why individuals may ignore their professional or personal responsibilities or why relationships between spouses or children and parents may fail to mature.

He also fails to commit himself with regard to the problem of postponing personal responsibilities. He vacillates between the importance of professional and personal responsibilities and says "Perhaps the solution lies instead in a dialectic that simultaneously embraces a deep-seated commitment to both professional and personal life. . . . There is a sense in which the building of a 'creative tension' between one's public and private lives results in greater contentment and well-being than a unifocal dedication to either." I find these concepts difficult to translate into specific behaviors that will assist one in establishing priorities or preventing personal or professional tragedies. His discussion of the establishment of priorities is even further removed from practical application since it is "derived from a context of true spirituality." I believe there are more understandable concepts to assist individuals in establishing priorities.

I *do* agree that the concept of quality time with children is a myth. However, I do not believe that "moments of joy and extraordinary closeness" are the basis for successful parent-child relationships and child rearing. The basis of success is the degree to which you can make that child feel special, loved, and respected. This will come only when the child knows he or she is one of your high priorities.

This subject matter has been developed into a course at Jefferson Medical College called "Personal Problems of Physicians," a 20-hour elective for second-year medical students. With regard to the competition between one's professional and personal lives, the following are some of the concepts discussed in that curriculum.

1. A percentage of marriage partners will have serious psychiatric disorders or personality problems. Rational principles for building and strengthening interpersonal relationships may not be successful with these partners. Recognition of the seriousness of the situation is the first step to possible resolution of problems.

2. One cannot treat all interpersonal relationships identically. Individuals come into a marriage with varied backgrounds and expectations. Therefore, preventive measures have to focus on the areas of greatest deficiencies in coping skills and on unrealistic expectations.

3. The most serious barrier to the development of mature and loving relationships between healthy spouses is a discrepancy in expectations and an unwillingness to discuss these differences and resolve them.

4. "Becoming a good doctor is, relatively speaking, an egocentric although respectable goal and that the most difficult and most important accomplishments in life are the development of giving relationships with other human beings, be they spouse, parents, children or friends."[2]

5. "When things go wrong at the interpersonal level the anguish and heartache are measurably greater than you will ever experience from disappointment in your profession."[2]

6. Physicians may learn, or be trained by their loved ones, that their medical responsibilities *can* be used to defer other responsibilities, whenever and wherever they choose, because families can easily be intimidated by the accusation that they are taking their spouse or parent away from a sick or dying patient.

7. While time management and organizational skills may be important in determining whether one is successful in his or her personal or professional life, they are secondary to commitment. It is much easier to be committed to the portion of your life that is filled with numerous short-term rewards. External recognition for developing mature and giving interpersonal relationships is meager

and long-term. The psychological basis of commitment has to be brought to consciousness. The saving grace is that commitment can be taught to the uncommitted.

These are just a few of the points we discuss in our elective course. The important point is that this is an extensive subject matter that has to be introduced to help physicians prepare for their personal and professional lives. As pediatricians, we believe in preventive medicine and, therefore, it is appropriate for this subject matter to be part of medical school education. It may prevent some family tragedies.

I am further indebted to Dr Boyce for one clever innovation. He says he has 18 years of parenting experience. I do not know whether he has 6-year-old triplets or 11- and 7-year-old children. But this innovative way of expressing parental experience permits my wife and me to now claim 317 years of parenting and grandparenting experience!

Robert L. Brent, MD, PhD
Department of Pediatrics
Jefferson Medical College
Philadelphia, PA 19102

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How Much Iron Is Enough?

Sir.—I write to take issue with the commentary by Finberg[1] in the November 1990 issue of *AJDC*. I do not agree that all infant formulas should have added iron. I say this for two reasons.

First, Finberg seems to assume that iron-fortified formula is the only source of iron for the infant and small child. All the cereals that I (and many others) have our patients start taking at age 2 months are now fortified. Meats are recommended by many of us at 4 months or even earlier. Many foods such as beans, nuts, and raisins have a high iron content. Most bread, macaroni, and spaghetti products are now iron fortified. So infants and toddlers get enough iron without fortifying their formulas.

Second, based on my experience, I disagree that extra iron gives no problems to a baby. Take an infant at 1, 2, or 3 months of age, as I have, who has been on a low-iron formula. Offer the mother three to four cans of an iron-enriched formula and ask her if she can see the difference. I have found many mothers who said "Iron gave gas and cramps; I had the same trouble when I had to take extra iron during my pregnancy!"

If what you advocate were true, I should have hundreds of anemic children in my practice—and I do not! My only rare patients with anemia are ones whose mothers keep on the bottle for over a year and take milk at the expense of a normal diet.

William B. Rogers, MD
1935 Second St
Cuyahoga Falls, OH 44221

1. Finberg L. Remembrance and loose ends of controversies past. *AJDC*. 1990;144:1188.

In Reply.—I am particularly pleased to respond to Dr Rogers' letter because he raises issues that are important and to which I believe there are completely satisfactory answers.

First, consider the issue of iron sources for most infants. Remember that we are here recommending a population approach that is appropriate as long as there is no harm and no excessive cost. The fortunate infants under Dr Rogers' care do not typify the population and most of them undoubtedly have done well with their iron nutrition. Many American infants are not offered fortified solid foods early on, and 10 or 15 years ago, this group had a very high incidence of iron deficiency. Some of those taking "low-iron" formulas still do. An analogy would be to oppose adding vitamin D to milk because many infants have enough sun exposure to avoid rickets.

Second, Dr Rogers raises the issue of symptoms experienced by infants taking iron-fortified milk. Objective studies[1] have shown that the symptoms are not related to the iron and occur no matter what feeding change is made and for the same number of infants. Thus, the symptom argument does not stand up under scrutiny.

Third, Dr Rogers states that he does not have "hundreds of anemic children" in his practice. I am sure he is correct; however, I believe that if he recommended fortified formula t overall prevalence of iron adequa would be even better.

Anemia is only one ill effect of ir deficiency. We can only know if I Rogers or others with similar situ tions have such indexes as transferr saturation, ferritin levels, and bo storage iron. Iron contributes to c lular function, probably to grow and possibly to both intelligence a resistance to infection, the last havi some exceptions of importance. Mo important in this context, though, a the inner city and rural poor who need for iron is more crucial.

Finally, no harm is done and t cost of this low but very usef amount of iron fortification is negl gible. I thank Dr Rogers for writin and allowing for greater explicatio

Laurence Finberg, MD
450 Clarkson Ave, Box 49
Brooklyn, NY 11203

1. Nelson SE, Ziegler EE, Copland A Edwards BB, Foman SJ. Lack of advers reactions to iron fortified formula. *Ped atrics*. 1988;87:360-364.

Acute Glossitis and Bacteremia Caused by *Streptococcus pneumoniae*: Case Report and Review

Sir.—Acute bacterial glossitis is a rar but extremely serious entity. To date only a handful of case reports hav appeared in the literature. A variet of causative organisms have bee identified, including three cases o acute glossitis resulting from *Haemophilus influenzae* type B,[1-3] two cases o suppurative glossitis from *Pseudomonas* species and hemolytic streptococci,[4] and one case of glossitis associated with *Trichomonas* species.[5] W report the first case, to our knowledge, of acute glossitis and associate bacteremia caused by *Streptococcu pneumoniae* to recognize this organism's role in this disease.

Patient Report.—A 28-month-old, previously healthy white boy presented to the clinic with a 1-day history of fever, cold symptoms, and mild crankiness. He refused any oral intake during the morning of his presentation. His mother noted rapidly progressive swelling of the tongue during the 3 hours prior to the office visit. No history of tongue trauma, toxin ingestion, or allergies was elicited. The patient's temperature was 39.6°C. The physical examination revealed a mildly

Reported Cases of Infectious Glossitis

Source, y	Patient Age	Causative Organism	Comment
Chandra and Prakash,[4] 1965	5 y 6 y	*Pseudomonas* species hemolytic streptococci	Suppurative parenchymatous glossitis requiring incision and drainage of residual abscesses (both cases)
Granoff and Nankervis,[1] 1976	14 mo	*Haemophilus influenzae* type B	Diffuse swelling of tongue and uvula; resembled angioneurotic edema
Edwards and Reynolds,[2] 1978	20 mo	*H influenzae* type B	Associated bacteremia; tongue excoriation present
San Joaquin et al,[3] 1980	4 y	*H influenzae* type B	Associated bacteremia
Brenner and Simon,[5] 1984	29 y	*Trichomonas* species	Communicated by orogenital sexual contact
Present report	28 mo	*Streptococcus pneumoniae*	Associated bacteremia

distressed boy with an enlarged, edematous, and erythematous tongue protruding slightly from his mouth. Involvement was greatest at the anterior aspect of the tongue. No evidence of laceration or trauma was observed. Phonation was normal and there was no evidence of stridor, dyspnea, or airway compromise. An otolaryngologist evaluated the child on his admission to the local hospital; there, the working diagnosis of tongue cellulitis was made. Blood cultures were obtained, and the child was given a dose of intravenous ceftriaxone sodium and was transferred to the Johns Hopkins Pediatric Intensive Care Unit, Baltimore, Md, for further treatment.

On his arrival at the unit, the child's temperature was 38.5°C and his respiratory rate was 20 to 30 per minute; profound drooling was observed. The anterior aspect of his tongue was diffusely enlarged, thickened, and erythematous. A few scattered vesicular lesions were noted on the tongue's ventral aspect. The patient's neck was supple, with marked bilateral, anterior cervical lymphadenopathy and left-sided posterior cervical lymphadenopathy. No cough, stridor, wheeze, or hoarseness was noted. Pulse oximetry demonstrated oxygen saturation of 97% to 100% in room air. Lateral neck roentgenograms showed a normal airway, pharynx, and epiglottis. The patient's white blood cell count was 24.7×10^9/L, with 0.47 neutrophils, 0.17 band forms, 0.21 lymphocytes, and 0.13 monocytes. Repeated blood culture, throat culture for group-A streptococci, and viral culture of the vesicular lesions were performed, the results of which were all negative, as were the results of an *H influenzae* type B latex agglutination assay of urine. The C1 esterase inhibitor level was normal.

On admission to the intensive care unit, the child's antibiotic therapy was changed to intravenous penicillin G potassium (250 000 U/kg per day) and cefuroxime sodium (150 mg/kg per day). He promptly defervesced, becoming afebrile within 12 hours after the onset of symptoms, and showed a rapid decrease in tongue swelling during the 24 hours following presentation. No subsequent complications were encountered. The original blood culture (obtained before antibiotics were administered) was positive for *S pneumoniae* after 24 hours. The child was discharged the following day.

Comment. — Few epidemiologic data are available on acute infectious glossitis (Table). Indeed, the available literature consists only of scattered case reports. Of those cases, the most common pathogen responsible for the infection is *H influenzae* type B. The authors' descriptions indicate that these cases were cellulitic and not pyogenic in nature. By contrast, Chandra and Prakash[4] described two instances in children of suppurative parenchymatous glossitis, resulting in abscess formation requiring incision and drainage; *Pseudomonas* species and hemolytic streptococci were the identified causative organisms in these cases. Finally, Brenner and Simon[5] reported *Trichomonas* species as the causative agent in a case of acute glossitis with prominent white plaques appearing in a 29-year-old man with a history of orogenital contact with a new sexual partner within the week before symptom onset.

To our knowledge, no other cases of pneumococcal glossitis have been reported. Clinically, our patient resembled the patient described by San Joaquin et al.[3] There was no obvious source of entry (tongue or mucosal or skin lesion) in either patient, and tongue swelling progressed rapidly. Because life-threatening respiratory impairment can develop rapidly in such cases, early recognition and prompt treatment are imperative. Treatment decisions in cases of acute glossitis should take into consideration *S pneumoniae* as a possible causative agent.

Jeffrey J. Stoddard, MD
Department of Pediatrics

Jayant K. Deshpande, MD
Department of Pediatrics
Department of Anesthesiology/
Critical Care Medicine
Johns Hopkins
Medical Institutions
600 N Wolfe St
Baltimore, MD 21205

1. Granoff DM, Nankervis GA. Cellulitis due to *Haemophilus influenzae* type B: antigenemia and antibody responses. *AJDC.* 1976;130:1211-1214.
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4. Chandra T, Prakash A. Suppurative parenchymatous glossitis. *Br J Surg.* 1965;52:234-235.
5. Brenner BE, Simon RR. Glossitis and dysgeusia. *Am J Emerg Med.* 1984;2:147.

Puncture Wound–Induced *Achromobacter xylosoxidans* Osteomyelitis of the Foot

Sir.—*Achromobacter xylosoxidans* is a gram-negative bacteria, found in the vertebrate intestinal tract and isolated from aqueous environments. The majority of infections caused by *A xylosoxidans* are either nosocomially acquired or involve immunocompromised hosts, but sporadic community-acquired infections in presumed normal patients have been described.[1]

Osteomyelitis of the foot following puncture wounds through sneakers is most often associated with *Pseudomonas aeruginosa* or other *Pseudomonas* species.[2-4] We describe a child with community-acquired *A xylosoxidans* osteomyelitis of the foot that resulted from a puncture wound.

Patient Report.—A previously healthy 11-year-old boy stepped on two nails 2.5

weeks before seeking care. The nails penetrated his tennis shoe to a presumed depth of about 2 inches. Immediately after the injury, the foot was soaked in hydrogen peroxide and alcohol. The wounds initially appeared to be healing well without evidence of drainage, pain, or swelling. In the week before admission the child complained of progressive, severe left foot pain. Several days before admission, swelling and a bluish discoloration of the sole of his foot just distal to one of the puncture wounds was noted.

On admission, the following were noted: temperature of 37.4°C and two puncture wounds on the plantar surface of his left foot, one of which was tender; the remainder of his physical examination was unremarkable. The peripheral white blood cell count was 11.1×10^9/L with 0.43 polymorphonuclear cells, 0.53 lymphocytes, and 0.04 monocytes. Wintrobe erythrocyte sedimentation rate was 12 mm/h. Roentgenography of the foot showed a lucency in the metaphysis of the left fifth metatarsal with associated soft-tissue swelling.

Blood cultures were obtained and therapy with intravenous ticarcillin disodium–clavulanate potassium (200 mg/kg per day) and gentamicin (7.5 mg/kg per day) therapy was begun; the child underwent surgical exploration of the wound within 24 hours. The fifth digital flexor tendon was necrotic; there was a lytic lesion in the fifth metatarsal that had broken through the plantar cortex. The bone was curetted, irrigated, and externally drained. Aerobic culture of the wound yielded coagulase-negative staphylococci. An oxidase-positive, gram-negative rod, subsequently identified as *A xylosoxidans*, was isolated from the bone specimen. This organism was resistant to gentamicin, tobramycin sulfate, and amikacin sulfate and sensitive to ticarcillin, trimethoprim-sulfamethoxazole, ticarcillin-clavulanic acid, and ceftazidime sodium. The child remained afebrile throughout his hospitalization. His foot swelling resolved by the fifth hospital day. Fourteen days after surgery, the erythrocyte sedimentation rate was 22 mm/h. He received ticarcillin-clavulanic acid and gentamicin after surgery for a total of 14 days and was discharged receiving oral trimethoprim-sulfamethoxazole therapy (16 mg/kg per day). At follow-up examination 2.5 months after surgery he was completely asymptomatic; roentgenographs showed periosteal reaction around the metaphysis of the fifth metatarsal.

Comment.—Achromobacter xylosoxidans is an aerobic gram-negative rod whose taxonomy remains in dispute. It is also known as *Alcaligenes dentrificans* subspecies *xylosoxidans* or *Achromobacter xylosoxidans* subspecies *xylosoxidans* and is listed in *Index Medicus* under *Alcaligenes*.[5] The organism has been recovered from a number of human sources including ear discharge; pleural and peritoneal fluid; urine; feces; cerebrospinal fluid; swabs of the eyes, ears, and pharynx; blood; prosthetic heart valves[1]; and bone.[6] It has also been isolated from numerous aqueous sources, including disinfectants commonly employed in hospitals.[1] Osteomyelitis due to *A xylosoxidans* is rare. To our knowledge, only one other case of *A xylosoxidans* osteomyelitis, in a patient with a fractured tibia, has been reported.[6]

Osteomyelitis of the foot following puncture wounds is usually caused by *P aeruginosa*, although infections with *Pseudomonas stutzeri* and *Pseudomonas maltophilia* have been described.[3,4] Our patient displayed the characteristics usually associated with *P aeruginosa*–induced osteomyelitis, including delayed symptomatology after puncture, lack of fever or systemic symptoms, and a normal white blood cell count. However, his erythrocyte sedimentation rate did not become elevated until 10 days after surgery.[7]

The most active antimicrobial agents against *A xylosoxidans* and nonaeruginosa *Pseudomonas* isolates appear to be the third-generation cephalosporins and trimethoprim-sulfamethoxazole. They are usually resistant to aminoglycosides and are variably susceptible to antipseudomonal penicillins.[8] Initial treatment of *P aeruginosa* osteomyelitis has generally included an aminoglycoside and antipseudomonal penicillin or a cephalosporin.[9] This may be inadequate therapy for *A xylosoxidans* infections and may lead to progression of disease or prolonged hospitalization. The duration of therapy of *A xylosoxidans* osteomyelitis of the foot awaits further definition.

As in our patient, it has been repeatedly demonstrated that sinus tract cultures do not reliably predict the causative agent of underlying acute or chronic osteomyelitis.[6,10] Bone cultures thus remain essential to determine antimicrobial therapy.

David M. Hoddy, MD
Department of Pediatrics
St Louis University School of Medicine
St Louis, MO 63104

Leslie L. Barton, MD
Department of Pediatrics
University of Arizona Health Sciences Center
Tucson, AZ 85724

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Condylomata Acuminata: Still Usually a Sexually Transmitted Disease in Children

Sir.—A number of points about the recent article by Boyd[1] on human papillomavirus (HPV) genital infections in children need to be made so that pediatricians and other concerned professionals, such as Family Court judges, are not confused or misled by this attempt at a "meta-analysis" of previous case reports.

First, as Disraeli once noted, "There are lies, there are damned lies, and there are statistics!" I have a very basic quarrel with Boyd's statistical analysis because he analyzes all cases together. One major question—how often condylomata acuminata are representative of sexual transmission, ie, sexual abuse in children—does not lend itself to this "lumping" of data.

To answer this important question, one must exclude children younger than age 1.5 years, since most of these cases are due to vertical transmission at or even before birth. One must also exclude teenagers, who may be having consensual sexual relations, and at any rate can give a clear history so that the mode of transmission is much less often an issue. When the denominator in Table 2[1] is thus revised, we have a sexual abuse reporting rate of 43% of the relevant cases of condylomata acuminata, a rate that is compatible with previous reports,[2] and not the very low and misleading 28% that Boyd reports.

Furthermore, the fact that a sexual mode of transmission cannot be clearly established in no way means that sexual transmission of wart virus did not occur! Children younger than age 7 years who are evaluated for sexual abuse often give unreliable histories due to fear, immaturity, or inadequate language. Boys are the worst at reporting and seldom reveal abuse at ages younger than 16 years,[3] even when confronted with incontrovertible evidence. For example, I reported a case of a 10-year-old boy with perirectal condyloma lata—proven syphilis—who refused to acknowledge what had happened to him despite our best efforts.[4]

Finally, I must take issue with Boyd's Table 3.[1] I can find no evidence from good, original sources to support the idea that HPV types 1 through 4 or 10 cause condylomata acuminata genital warts. No author or investigator I have known in the past 6 years has ever detected DNA from these subtypes in any clinical specimens from perineal or rectal area condylomata acuminata, in either adults or children. If Boyd knows of such data, I would appreciate references to *primary sources* that he believes are authoritative and use good methods. I previously pointed out[5,6] possible methodologic errors in an often-quoted 1980 study.[7] This report, which I once quoted in a review[8] before realizing its flaws, exemplifies why reliance on critically and meticulously reviewed original reports is essential when developing references in this extremely difficult and potentially controversial field of investigation.

Therefore, I must emphasize that Boyd's analysis should be viewed with skepticism if he intends us to conclude that nonsexual transmission of HPV takes place with any degree of commonness. It clearly can happen,[9] but under very circumscribed clinical circumstances.[5,6] I stick strongly to my position (also taken by other experts[10]) that there is only rare evidence of nonsexual transmission of condylomata acuminata–type warts.[5,6,8] I have previously suggested a clinical scheme for determining whether warts in the rectoperineal area in children are probably sexually transmitted and should be reported for investigation.[6]

John M. Goldenring, MD, MPH
245 Terracina Blvd, No. 202
Redlands, CA 92373

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In Reply.—I would like to thank Dr Goldenring for his careful analysis of my article. Although I am unsure of the exact meaning of "meta-analysis" in this context, I can assure him that, like most retrospective analyses of the literature, this project was undertaken with the desire to better define the picture, not muddy the waters. It was never my intent to assess the problem with a statistical analysis; otherwise, inferences would have been made from them. These figures are simply a compilation of what is present in the literature.

Goldenring seems to intimate that the percentage of children who acquire venereal warts from molestation is much higher, an opinion not held by all experts and for which significant evidence to the contrary now exists.[1,2] Cohen et al[1] evaluated 73 children with anogenital warts and concluded that fewer than 10% had been sexually abused. Likewise, Obalek and coworkers[2] recently reported that of 32 children with condylomata acuminata, only one (3%) was suspected of having been molested. It appears that the 28% figure cited in my article may be more accurate than Goldenring acknowledges.

Eliminating children younger than age 1.5 years and teenagers will certainly lessen the pool of patients to analyze, but it may also exclude some patients. Most, but not all, children younger than 18 months probably do indeed acquire their lesions by vertical transmission.[3-5] Goldenring's statement, ". . . the fact that a sexual mode of transmission cannot be clearly established in no way means that sexual transmission of wart virus did not occur!" should be taken *prima facia*. The 37% of the cited cases in which the infection was acquired by unknown means are simply that, cases in which the authors failed to discover a means of infection.

Finally, Goldenring takes issue with Table 3 in which HPV types 1, 2, 6, 10, 11, 16, and 18 are cited as being associated with anogenital warts. The types he questions the most, 1, 2, and 10, were cited by a group of investigators[6] who included those types on a table in their article. On more careful inspection of their references, I was unable to find documentation for the discovery of condylomata acuminata with these HPV types. However, the authors of the two previously cited reports,[1,2] as well as our clinic, have found "nonclassical" HPV types, *including* type 2, in cases of pediatric venereal warts. Those who also "stick strongly" to Golden-ring's position that ". . . there is only rare evidence of nonsexual transmission . . ." for anogenital warts may want to reexamine their views in light of the recent evidence to the contrary.

Alan S. Boyd, MD
Department of Dermatology
Texas Tech University
Health Sciences Center
Lubbock, TX 79430

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Lead Poisoning in Children With Developmental Disabilities

Sir.—We were pleased to read the article by Friedman and Weinberger[1] in the September 1990 issue of *AJDC* regarding the screening, diagnosis, and treatment of children with lead poisoning. We describe a child with mental retardation whose pica behavior led to lead poisoning.

Patient Description.—An 8-year-old boy with previously diagnosed infantile autism and mental retardation underwent interdisciplinary team evaluation. The medical history incorporated questions regarding stereotypic behaviors, specifically pica. With confirmation of pica, a lead level of 3.13 μmol/L and an erythrocyte protoporphyrin level of 364 μg/dL were measured. Lead-based paint was discovered in the home of the boy's grandparents. He received chelation treatment with intramuscular calcium disodium ethylenediaminetetraacetic acid (EDTA) and oral penicillamine on an outpatient basis. His lead level dropped to 1.45 μmol/L. Repeated developmental testing 4 years later showed performance at the 8-month level in language skills and at the 2- to 3-year level in other skills. The patient's lead level at that time was 2.41 μmol/L, with an erythrocyte protoporphyrin level of 90 μg/dL. Pica behavior was still present.

What Can We Learn From This Patient?—Children and adults with developmental disabilities including autism and mental retardation, regardless of cause, can display behaviors inappropriate to their chronologic ages. These behaviors can be stereotypic or can result from associated medical problems such as iron deficiency. Other features of developmental disorders, such as overactivity and cognitive and motor abnormalities, can obscure the clinical signs of lead poisoning. The prevalence of pica behavior in groups of persons with severe and profound retardation ranges between 5% and 15%.[2,3]

Physicians, family members, and others involved in the care of persons with developmental disabilities should not fail to consider the presence of pica behavior in such individuals. Lead poisoning and other associated problems, such as parasitic infection and foreign body ingestion, are potential causes of additional disabilities that are reversible.

Stephen B. Sulkes, MD
University Affiliated Program
for Developmental
Disabilities
University of Rochester
Medical Center
Rochester, NY 14642

Dennis W. O'Connor, MD
Keuka Family Practice
Associates
Bath, NY 14810

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Neurodevelopmental Outcome of Offspring of the Diabetic Mother: Need for Further Research

Sir.—The improved care of diabetic women prior to conception and during pregnancy has significantly decreased the incidence of mortality, morbidity, and congenital anomalies in the infants of these diabetic mothers.[1-3] However, postnatal complications still occur more frequently among these infants than among infants of nondiabetic mothers.[4-8] The significance of these complications for the developing child of the diabetic mother must be established to determine whether the complications at birth predispose these children to later neurodevelopmental dysfunction.

An analysis of the results of follow-up studies of children whose mothers had diabetes during pregnancy should address this issue. Results of five major follow-up studies have been published between 1977 and 1988.[9-13] However, the results have often been contradictory and limited by methodologic flaws. For example, only two of the studies employed control groups.[12,13] In all the studies, sample sizes were relatively small (73 to 174 children) and attrition rates were high (15% to 42%). The high mortality rates (ranging from 7% to 14%) combined with the relatively high attrition rates make inferences based on the findings problematic, since only 58% to 85% of the cohorts were actually evaluated.

The variability of the study designs further confounds comparisons between studies. The instruments used to evaluate outcome included standardized intelligence tests,[9,10] a developmental screening device,[13] and behavioral questionnaires.[11,12] Conclusions based on the data collected were often inconsistent and contradictory. For example, Stehbens et al[9] found impaired intellectual functioning among 5-year-old children of diabetic mothers who were small for gestational age or whose mother's pregnancy was complicated by acetonuria. On the other hand, Persson and Gentz[11] found no relationship between maternal acetonuria and intelligence. Cummins and Norrish[10] reported a normal distribution of intellectual functioning among children of diabetic mothers. Petersen et al[13] determined a relationship between early intrauterine growth delay and lowered developmental scores among children of diabetic mothers.

Similar contradictory results were reported in studies focusing on behavioral data. Persson and Gentz[11] determined that diabetic mothers under high stress reported more behavioral problems among their children. Hadden et al[12] found no differences between the emotional or academic status of children of diabetic mothers and a matched group of children of nondiabetic mothers.

To our knowledge, no one study has comprehensively evaluated neurologic, intellectual, and behavioral outcomes of children of diabetic mothers with a sufficiently large population and a matched control group. Explicit data on maternal pregnancy and newborn outcome, appropriate control groups, large sample size, and a broad range of tests of neurologic, intellectual, and behavioral functioning at school ages are needed to attempt any attribution to the diabetic pregnancy per se. It is yet unclear whether the influence of the diabetic state in pregnancy produces subtle developmental dysfunctions. This can only be detected through a thorough evaluation of the child in a wide range of areas. If it is determined that the child of the diabetic mother is at greater risk for subtle dysfunctions, this child must be followed up closely from birth. Early detection is critical so that remedial programs can be developed and implemented to prevent the predisposition from becoming a precursor for major developmental and learning handicaps.

ESTHER GOLDSTEIN, PHD
Department of Education
Center for Child Development
BASIL PORTER, MBBCH
AHARON GALIL, MD
Center for Child Development
Soroka University Hospital
Ben Gurion
University of the Negev
PO Box 151
Beer Sheva, Israel 84110

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Albuterol Inhalations in Acute Chest Syndrome

Sir.—Recently we treated a 12-year-old boy with sickle cell anemia and acute chest syndrome (ACS) who had decreased air entry in the same way an asthmatic patient does. This prompted us to treat him with nebulized albuterol, which improved his dyspnea and aeration. Finding no reports of β_2 agonist use in acute chest syndrome we performed the following preliminary study to determine if albuterol inhalation therapy could be a useful adjunct in the treatment of ACS in sickle cell anemia.

Patient Reports.—Four patients, including the aforementioned one, all with ACS and sickle cell anemia, were evaluated. None had a personal or family history of asthma or wheezing. Each was at least 8 years old, enabling use of the Wright peak flow meter. Initially each patient had chest pain, difficulty breathing, decreased breath sounds and/or crackles on chest auscultation, and roentgenographic evidence of an acute pulmonary infiltrate. Each was thus diagnosed as having ACS.

The four patients received conventional treatment for ACS, including oxygen, intravenous fluids, antibiotics, and in two cases, exchange transfusions. Each child also received 0.02-mL/kg albuterol sulfate (5 g/L) via 15-minute nebulization. Peak expiratory flow rate was measured before and after each albuterol treatment. Two or three measurements were taken before and after inhalation, thus making improved technique an unlikely cause of peak flow increase. A 15% increase in peak flow was considered a significant positive response.

All four patients in this survey had positive responses. Their improvement was greater earlier in the course of their illness, and lessened as their signs and symptoms of pulmonary disease diminished. The Table shows the maximum increase in peak flow for each patient following albuterol inhalation. Each child tolerated the therapy without ill effects, and no child failed to respond positively to the treatment.

Repeated peak flow determinations before and after bronchodilator treatments were performed at follow-up visits in all four children at least 8 weeks after recovery from ACS. All showed no significant (less than 15%) peak flow increase after nebulization. This, plus the lack of wheezing or asthma history discounts preexisting reactive airway disease as a basis for the response to albuterol.

Comment.—Based on these preliminary findings, a double-blind placebo-controlled study is needed to evaluate the potential role of al-

Maximum Peak Flow Increase After Albuterol Treatment

Patient No.	Pretreatment Peak, L/min	Posttreatment Peak, L/min	% Increase
1	85	170	100
2	50	95	90
3	230	300	30
4	50	150	200

buterol in the treatment of acute chest syndrome.

Edward Handelsman, MD
Department of Pediatrics
Schneider Children's Hospital
Long Island Jewish
Medical Center
New Hyde Park, NY 11042
Debra Voulalas, MD
Children's Seashore House
Children's Hospital of
Philadelphia
Philadelphia, Pa

Penile Vasculitis With Impending Necrosis Treated With Prostaglandin E$_1$ Infusion

Sir.—Prostaglandin E$_1$ (PGE$_1$) infusions have been used in the treatment of occlusive vascular diseases since 1973, when Carlson and Eriksson[1] described subjective improvement in three of four patients with peripheral atherosclerotic vascular disease and ischemic rest pain given PGE$_1$ by femoral artery infusion. Since that time, PGE$_1$ has been reported to be effective in Raynaud's syndrome, peripheral vascular occlusive disease, and Kawasaki's disease.[2-4] We report the dramatic clinical reversal of severe, apparently immune complex–mediated vasculitis of the penis following the use of intravenous PGE$_1$ in an 8-year-old boy.

Patient Report.—An 8-year-old black boy presented to the UCLA Medical Center in 1981 with a 1-day history of severe pain and swelling of his penile shaft. He had no other somatic complaints, gave no history of recent febrile illness, and was able to void without difficulty on admission.

The patient had a complex medical history, including hereditary spherocytosis, tetralogy of Fallot with surgical correction at age 5 years, and intermittent bloody diarrhea of unclear origin that began at age 2 years. In addition, he had multiple episodes of peripheral vasculitis leading to the partial or complete amputation of several digits on his hands and feet. An exhaustive effort had been made to elucidate the origin of the vascular disease, and the only consistent finding had been a rise in the level of circulating immune complexes at the onset of symptoms, and a fall with their resolution. Unfortunately, no pathologic information from the previously amputated digits was available, and although an attempt had been made to perform a biopsy on an artery, it was unsuccessful.

On earlier occasions a variety of therapeutic interventions had been used, including dextran-40, aspirin, dipyridamole (Persantine), intra-arterial reserpine, corticosteroids, and plasmapheresis. There had been a modest response to corticosteroid therapy in conjunction with plasmapheresis, but each episode had led to some degree of amputation.

Physical examination revealed an afebrile, thin, black child whose penis was markedly swollen, although not erect, with marked ecchymosis of the entire shaft and moderate tenderness. The foreskin was edematous and phymotic. His testes were descended bilaterally, and he had a normal scrotal sac. A 3 × 4-cm ecchymotic area was noted over the lateral malleolus of the left leg. Results of admission laboratory studies were essentially normal with the exception of increased immune complexes at a level of 730 mg/L (normal, up to 310 mg/L) by polyethylene glycol precipitation.

Because of concern over the possibility of necrosis with amputation of the penis, PGE$_1$ was administered in an emergency investigational new drug protocol beginning approximately 2 hours after admission. In addition, due to a modest previous response to steroids, hydrocortisone (500 mg, intravenous bolus) was administered on day 1 of his PGE$_1$ infusion, and continued as prednisone (20 mg by mouth) once daily for the next 3 days.

The patient started receiving a continuous intravenous PGE$_1$ infusion (0.5 mg per 200 mL of 5% dextrose solution) at a rate of 0.007 μg/kg per minute, and this was increased over the next 5 hours to a rate of 0.02 μg/kg per minute. The patient received a total dose of 2296 μg or 112 μg/kg over 92 hours, without any discernible side effects. Four hours after beginning the infusion, the patient noted a marked decrease in pain and an associated slight decrease in penile swelling. By day 2 the swelling was notably reduced, and by day 3 the swelling had completely resolved. By the time the PGE$_1$ infusion was completed on day 4, the ecchymosis of the penile shaft, and over the left lateral malleolus had disappeared, and the patient had entirely normal genital urinary examination results. At this point the level of circulating immune complexes was 350 mg/L. He made a complete and uneventful recovery and has not suffered from symptomatic vasculitis in the last 9 years.

Comment.—PGE$_1$ affects platelet aggregation and peripheral vascular tone, and has been used in the treatment of both Raynaud's syndrome and peripheral vascular disease, with dramatic benefits in some but not all patients. Recently, PGE$_1$ has been used to improve renal blood flow after kidney transplantation (Allen Wilkinson, MD, personal communication, March 1990), and to decrease pulmonary vascular resistance after heart transplantation.[5] A recent case report describes a striking reversal of peripheral ischemia of the hands of an infant with Kawasaki's disease.

We noted dramatic improvement in our patient within 4 hours after PGE$_1$ infusion was started, and a full recovery 4 days later. This response may well have been due to vasodilation and/or inhibition of platelet aggregation. However, work by McLeish et al[6] and others has demonstrated that PGE$_1$ infusion leads to a reduction in immune complex deposition and in the synthesis of the specific antibody responsible for this deposition in a murine model for immune complex– mediated glomerular nephritis. Although only a speculation, PGE$_1$ may have had an immune-modulating effect in this patient as well, outlasting its temporary effect on platelet aggregation, and vascular tone. Prostaglandin E$_1$ is currently only licensed for use in maintaining the patency of the ductus arteriosus in congenital heart disease. Although its value is unproven, we suggest that PGE$_1$ treatment may be of benefit in selected patients with vascular disease unresponsive to other therapies.

Anthony A. Horner, MD
Karen Dunn, MD
E. Richard Stiehm, MD
UCLA Medical Center
Los Angeles, CA 90024

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THE EDITORIAL BOARD SPEAKS...

Losing Time

Albert W. Pruitt, MD

"Al" has been the mainstay of the editorial board for pharmacologic and toxicologic information. Despite his heavy academic and administrative load, Al has actively reviewed for us and has participated in all phases of the board's activities.

Most recently, he participated in the Advanced Management Program of the Harvard Graduate School of Business in Boston, Mass. He also participated in the Program in Clinical Effectiveness of the Harvard School of Public Health, covering such areas as biostatistics, epidemiology, and health policy and management. These experiences served to broaden his administrative experience and skills.

He remains the Ellington Charles Hawes Professor and Chairman of the Department of Pediatrics, Medical College of Georgia, positions he has held for more than 10 years. He also served as interim dean of the School of Medicine of the Medical College of Georgia from 1985 to 1986, and again in 1988. His professional activities have included the following: chairmanship of the Committee on Substance Abuse of the American Academy of Pediatrics (1990 to present); member of the Physician Task Force, National Training Systems, Office for Substance Abuse Prevention (1990 to present); member of the Pediatric and Adolescent Medicine Committee of the National Council of Juvenile and Family Court Judges (1990 to present); member of the Steering Committee of the Georgia General Assembly's Conference on Children of Cocaine and Substance Abuse (1990); and member of the National Advisory Council on Maternal, Infant and Fetal Nutrition of the US Department of Agriculture (1990 to present).

After his release from prison, "Johnny" learned quickly that no one would hire him if he admitted to his record, so he stopped letting prospective employers know of it and got a job repairing engines. For a few months, he worked successfully and contentedly. When the boss found out about the prison record, he promptly fired young Johnny. There was no one to whom Johnny could turn for counsel, advice, or help of any kind. Whatever help Johnny was entitled to along those lines he had already received while "behind the fence." Sooner, rather than later, Johnny was once again back there.

This little story, with its accompanying emotion and attempt at justification, is one I know to be true; I am acquainted with Johnny. However, it is also a generic tale of young men, boys really, who do time early in their lives. We all acknowledge the need to identify those youngsters who are at risk of becoming Johnny, but judging from their health status at the time of arrest, most have not been in our offices. The prison population of incarcerated youth is increasing rapidly and sharply in almost every state, largely due to drug-related crimes. Many factors contribute to the growing number of "Johnnies" today, young men who are incarcerated at an early age and therefore often released at an age at which they should have several decades of productivity left. How hollow is that prospect in reality? For many, release from prison is really only an intermission in a life that, after the first incarceration, is almost certain to be spent largely in prison. The mere fact of having "done" time is almost a curse that means the experience will be repeated, in many cases, many times.

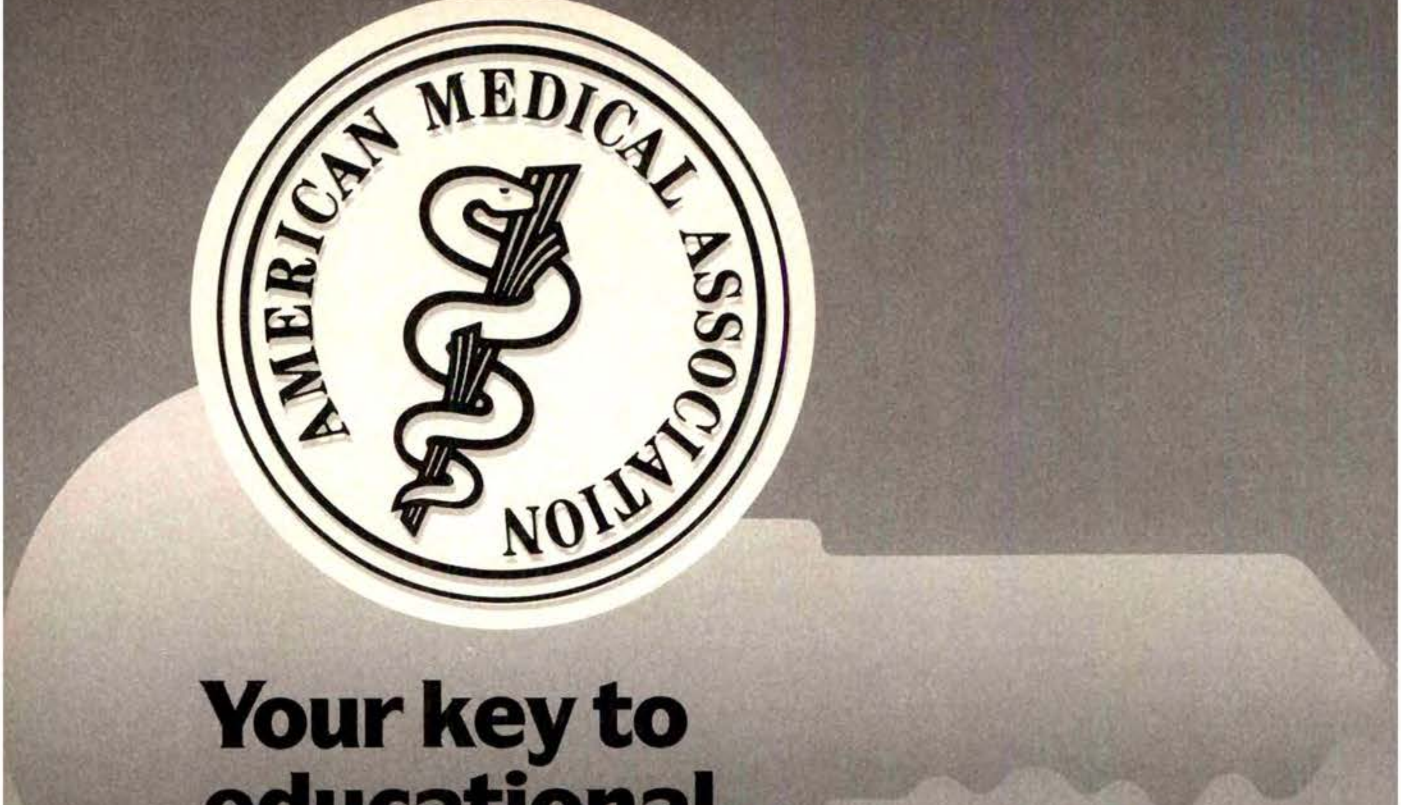
One view, of course, is to say that these young men deserve what they get and get what they deserve. There is at least some truth to this. They have broken the law and have committed acts that are dangerous and destructive to other people and to the fabric of society. However, I have made two observations that I would like to share: the first is about what some of these young men are like, and the second is about what exactly the punishment may amount to.

For the past few years, I have been permitted to get to know a large number of young men and older men in a nearby state prison. Being with both age groups is important because meeting "John," who was "Johnny" decades ago, only intensifies my concern about what time holds for incarcerated youth. One can be certain that John's story is known by every Johnny, and those stories do not help.

So what is this Johnny like? Who are these young guys so probably "sentenced to life" just because they are doing time? The thing that I found truly shocking initially, and that continues to astonish me every time I face it, is that these young men are so utterly familiar to me. They are by no means a different breed. They are neither especially vicious nor especially hotheaded. They are neither particularly unwise nor particularly cunning. They are no more open or more closed than the house officers with whom I work.

The one thing that sets these young men apart from those on the outside is how scared they are. They are scared about what has happened to them, about what it all means, and about who they themselves are becoming as they look at John. They are scared about the short term, and very tense and frightened about what will happen "when I get out."

Their anxiety about the future is all too well founded and relates to my second observation. Despite all the attempts to make the time in prison in some way productive and corrective through education, job training, personal rehabilitation, health care, and so forth, there is no room for many of these young men when they come out. Very often there is no room in their families, who are disgraced and disgusted by them; there is no room in the work force, in which they are regarded as poor risks, undeserving of help, or deserving of further punishment. Most of all, however, there is no room for these young men in our society's collective heart, so filled are we with fear of them. Unless we can somehow change that feeling, these men are condemned to a life of "losing time."



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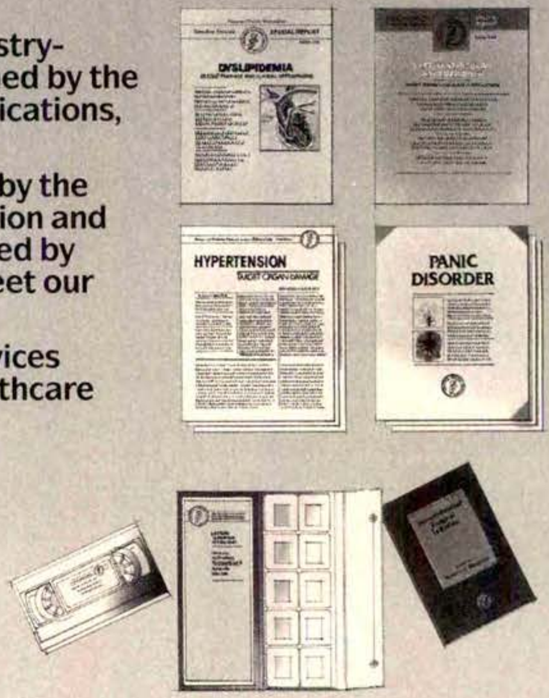

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EDITORIAL

Parental Alcoholism

A Neglected Pediatric Responsibility

Despite the high prevalence of parental alcoholism and its many serious consequences, pediatricians have little awareness of the drinking problems in the families of the patients they treat.

The article by Duggan et al[1] in this issue of *AJDC* speaks for itself. My comments only underscore the points these authors have made so well. Particularly important is the question "Why?" Why do pediatricians do such a poor job of recognizing alcohol problems? Implicit in the article and my comments is a plea; a plea to do a better job.

See also p 613.

The findings of Duggan et al should come as no surprise. Fewer than half of US medical schools provide any formal instruction in alcohol or drug treatment.[2] The findings highlight the sorry state of physician interest in and involvement with the major health problems associated with alcohol use.

When the families of 147 pediatric inpatients aged 10 years and older were interviewed, 22 families (15%) screened positive for alcoholism. Only one of the 22 families had been identified by an attending pediatrician. The pediatric house staff had identified no one. Other departments at the same institution did considerably better. Psychiatric attending physicians correctly identified 65% of alcoholic family members, and psychiatric house staff, 66%. For medicine, the rates were 35% and 52%, and for surgery they were 35% and 20%, respectively. Only obstetricians approached the low pediatric rates.

Why is this? Is it because of a lack of knowledge, or is it because of a feeling that parental drinking is none of the pediatrician's business? Do physicians feel uncomfortable about what may be perceived to be an issue that is too personal to discuss? The answer is probably some combination of all of the above.

Biomedical research advances have fueled a tremendous expansion of our clinically relevant knowledge base. Because so much worthwhile information has been generated, subjects must fight for inclusion in the course of medical studies.

How much do we really need to know? Most of the information necessary to recognize and intervene with families troubled by alcoholism is not hard to come by. Nor does it require a great deal of curriculum time. It might, however, require the recruitment and training of qualified instructors. Harder to accomplish is the instillation of a sense that alcohol abuse and alcoholism are medical problems that physicians should become involved with. At a minimum we should know the following: (1) Many parents are alcohol abusers and alcoholics. (2) Parental alcoholism may have many serious consequences for children. (3) Screening for parental alcoholism is easy and quick. (4) Intervention can make a difference. (5) Physicians need to know how to overcome feelings of discomfort in dealing with alcoholic parents.

Many Parents Are Alcohol Abusers and Alcoholics

The 15% prevalence rate of alcoholism found by Duggan et al[1] agrees with national estimates of 13.5% lifetime prevalence rates of alcohol abuse and alcoholism in the general population.[3] It also agrees with the estimates that one in eight American children has alcoholic parents.[4]

Parental Alcohol Abuse and Alcoholism Can Have Many Serious Consequences for Children

These consequences include highway deaths, child abuse, fetal alcohol syndrome, and an increased incidence of alcoholism and other drinking problems in children of alcoholics. Consequences also include dysfunctional family life that may be chaotic, nonsupportive, and abusive.[5] Pediatricians generally do know these things, but for reasons that are far from clear do not usually become involved.

Perhaps the most obvious consequence of parental drinking is death on the highway. Each year more than 40 000 Americans die in traffic accidents. More than 8000 of these deaths are in the pediatric age range. Estimates are that drunken driving accounts for more than 60% of these fatalities. Hundreds of thousands more suffer serious injuries because of automobile accidents.[6]

Another major consequence of parental drinking is child abuse. Pediatricians, who are such strong advocates of child protection and child abuse regulations, have not as a rule made the link between parental drinking and child abuse; however, there is a link. A significant number of child abusers are alcohol abusers as well.[7] Whether it be physical abuse, incest, neglect, abandonment, or emotional abuse, child abuse is an important pediatric issue.

Pediatricians are familiar with fetal alcohol syndrome and know that it is caused by maternal drinking. Failure to obtain an adequate family history, however, robs the pediatrician of the opportunity to detect maternal alcohol abuse and to initiate action to prevent problems in unborn children. The fact that obstetricians do such a poor job of recognizing alcoholism makes pediatrician involvement even more important.

Still another problem is that children of alcoholics are at increased risk of becoming problem drinkers themselves. Genetic and environmental factors may both play a role.[8] The road to adult alcoholism usually begins in adolescence when abuse can be particularly disastrous. The three leading causes of death in the 15- to 24-year-old age range are accidents, suicide, and homicide. All three are frequently associated with the abuse of alcohol.

Alcohol abuse in adolescence does more than kill. There may be learning problems, emotional problems, and delayed, inadequate, or abnormal development of relationships with family, friends, and dating partners.[5]

Screening for Alcoholism Is Easy and Quick

Families generally do a good job of hiding their alcohol problems. Pediatricians must make a conscious effort to identify these problems or they will be missed. Fortunately, there are readily available screening tests that are easy and quick to administer. It should not take more than 10 minutes to complete the short version of the Michigan Alcohol Screening Test and the CAGE, used by Duggan et al.[1]

Intervention Can Make a Difference

If physicians do not believe anything can be done for the child of an alcoholic or for the drinking parent, then there is little therapeutic reason for obtaining a history except to explain current problems or to predict future problems. If we know that alcoholics can be treated and do recover, we will realize that medical histories are essential. Pediatricians should know which treatment methods work and how to use locally available resources.

Treatment of adult alcoholics has a 50-year history of success. That success began far outside the medical mainstream. Two alcoholics, one of them a physician, formed a fellowship of alcoholics that we know today as Alcoholics Anonymous. Medical acceptance of the principles of Alcoholics Anonymous was late in coming, but today few alcohol treatment programs do not include at least some of its principles. Many are based almost entirely on Alcoholics Anonymous.

How to Overcome Feelings of Discomfort in Dealing With Alcoholic Parents

A 1988 survey of pediatric faculty and house staff revealed that 33% of the faculty and 25% of the house staff felt little or no responsibility for referring patients' family members with alcohol problems.[9] Why is this?

Perhaps it is that pediatricians feel uncomfortable asking people about their drinking habits. Should they? There is precedent for asking questions in potentially sensitive personal areas. For example, few physicians feel any discomfort asking people about their bowel habits. Even once taboo questions about sexual practice are becoming accepted as part of what a physician is expected to ask. Questions about the use of alcohol and other drugs are more than appropriate.

Perhaps it is the fear of confrontation. It is not easy to suggest that someone has a drinking problem. Denial is to be expected and anger is common. However, with training and practice, intervention can be successful.[10] For those who are untrained, referral is appropriate. Few communities do not have someone skilled at intervention.

Putting it all together means knowing that there is a problem and learning how to manage that problem. Even if no intervention is planned, knowledge of alcoholism is an important component of understanding family dynamics. The article by Duggan et al[1] lays the groundwork. Now, it is up to those who take responsibility for children's health to act responsibly.

Donald Ian Macdonald, MD
Employee Health Programs
6550 Rock Spring Plaza
Suite 280
Bethesda, MD 20817

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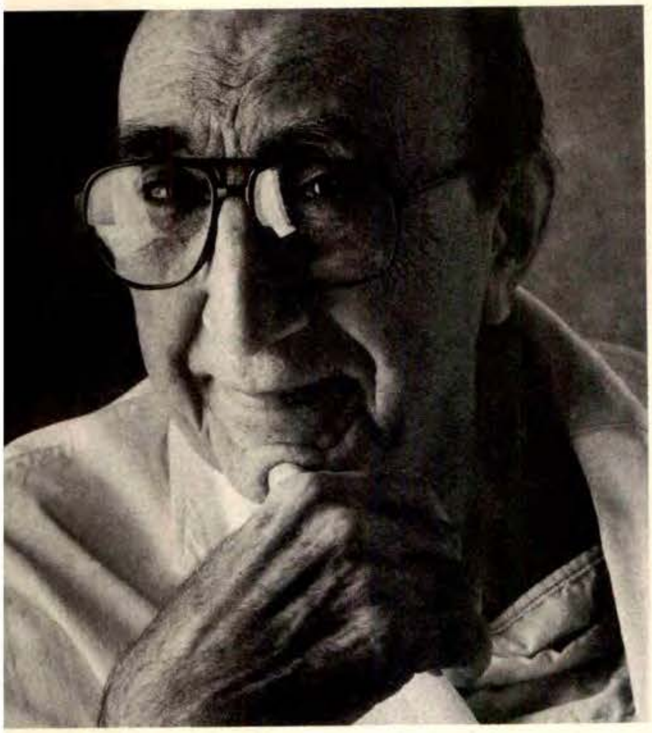

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CONTRAINDICATIONS: Patients hypersensitive to ibuprofen or patients with all or part of the syndrome of nasal polyps, angioedema, and bronchospastic reactivity to aspirin or other nonsteroidal anti-inflammatory agents. Anaphylactoid reactions to ibuprofen have occurred in such patients.

WARNINGS: Risk of GI Ulcerations, Bleeding, and Perforation with NSAID Therapy: Physicians should remain alert for ulceration and bleeding in patients treated chronically with NSAIDS even in the absence of previous GI tract symptoms. In patients observed in clinical trials of several months' to two years' duration, symptomatic upper GI ulcers, gross bleeding or perforation appear to occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for one year.

Except for a prior history of serious GI events and other risk factors known to be associated with peptic ulcer disease, no risk factors have been associated with increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less well than other individuals and most spontaneous reports of fatal GI events are in this population.

PRECAUTIONS: General: Because serious GI tract ulceration and bleeding can occur without warning symptoms, physicians should follow chronically treated patients for the signs and symptoms of ulceration and bleeding.

Blurred and/or diminished vision, scotomata, and/or changes in color vision have been reported. If a patient develops such complaints the drug should be discontinued and the patient should have an ophthalmologic examination.

Fluid retention and edema have been reported with ibuprofen; therefore, the drug should be used with caution in patients with a history of cardiac decompensation or hypertension.

Ibuprofen can inhibit platelet aggregation and prolong bleeding time. CHILDREN'S ADVIL® SUSPENSION should be used with caution in persons with intrinsic coagulation defects and those on anticoagulant therapy.

The antipyretic and anti-inflammatory activity of ibuprofen may reduce fever and inflammation, thus diminishing their utility as diagnostic signs in detecting complications of presumed noninfectious, noninflammatory painful conditions.

Small decreases (usually not exceeding one gram) in hemoglobin and hematocrit with an apparent dose response relationship have been observed following chronic administration. If there are no signs of bleeding, it is probably not clinically important.

To avoid exacerbation of disease or adrenal insufficiency, patients on prolonged corticosteroid therapy should have their therapy tapered slowly when CHILDREN'S ADVIL® SUSPENSION is added to the treatment program.

Aseptic meningitis: Aseptic meningitis with fever and coma has been observed on rare occasions in adult patients on ibuprofen therapy. Although it is more likely to occur in patients with systemic lupus erythematosus and related connective tissue diseases, it has been reported in adult patients who do not have underlying chronic disease. If signs or symptoms of meningitis develop in a patient on CHILDREN'S ADVIL® SUSPENSION, the possibility of its being related to ibuprofen should be considered.

Renal Effects: As with other nonsteroidal anti-inflammatory drugs, long-term administration of ibuprofen to animals has resulted in renal papillary necrosis and other abnormal renal pathology. In humans, there have been reports of acute interstitial nephritis with hematuria, proteinuria, and occasionally nephrotic syndrome.

A second form of renal toxicity has been seen in patients with prerenal conditions leading to reduction in renal blood flow or blood volume. In these patients, administration of a nonsteroidal anti-inflammatory drug may cause a dose dependent reduction in prostaglandin formation and precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, and those taking diuretics and the elderly. Those patients at high risk who chronically take CHILDREN'S ADVIL® SUSPENSION should have renal function monitored if they have signs or symptoms of azotemia. Discontinuation of nonsteroidal anti-inflammatory drug therapy is typically followed by recovery to the pretreatment state.

Since ibuprofen is eliminated primarily by the kidneys, patients with significantly impaired renal function should be closely monitored and a reduction in dosage should be anticipated to avoid drug accumulation.

Information for Patients: Physicians may wish to discuss with their patients the potential risks and likely benefits of treatment with CHILDREN'S ADVIL® SUSPENSION.

Laboratory Tests: Meaningful (3 times the upper limit of normal) elevations of SGPT or SGOT (AST) occurred in controlled clinical trials in less than 1% of patients. A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of more severe hepatic reactions while on therapy with ibuprofen. If abnormal liver tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur, CHILDREN'S ADVIL® SUSPENSION should be discontinued.

Diabetes: Each 5 mL of CHILDREN'S ADVIL® SUSPENSION contains 2.5 g of sucrose which should be taken into consideration when treating patients with impaired glucose tolerance. It also contains 350 mg of sorbitol per 5 mL. Although in clinical trials CHILDREN'S ADVIL® SUSPENSION was not associated with more diarrhea than control treatments, should a patient develop diarrhea, the physician may wish to review the patient's dietary intake of sorbitol from other sources.

Drug Interactions: *Coumarin-type Anticoagulants:* Bleeding has been reported when ibuprofen and other nonsteroidal anti-inflammatory agents have been administered to patients on coumarin-type anticoagulants; the physician should be cautious when administering CHILDREN'S ADVIL® SUSPENSION to patients on anticoagulants.

Aspirin: Concurrent use of aspirin is not recommended.

Methotrexate: In vitro studies indicate that ibuprofen could enhance the toxicity of methotrexate. Caution should be used if CHILDREN'S ADVIL® SUSPENSION is administered concomitantly with methotrexate.

H_2 Antagonists: In studies with human volunteers, coadministration of cimetidine or ranitidine with ibuprofen had no substantive effect on ibuprofen serum concentrations.

Furosemide: Ibuprofen can reduce the natriuretic effect of furosemide and thiazides in some patients. During concomitant therapy with CHILDREN'S ADVIL® SUSPENSION, the patient should be observed closely for signs of renal failure as well as to assure diuretic efficacy.

Lithium: Ibuprofen produced an elevation of plasma lithium levels (15%) and a reduction in renal lithium clearance (19%) in a study of 11 normal volunteers during the period of concomitant drug administration. Patients should be observed carefully for signs of lithium toxicity. Read package insert for lithium before its use.

Pregnancy: Administration of ibuprofen is not recommended during pregnancy or for use by nursing mothers.

Infants: Safety and efficacy of CHILDREN'S ADVIL® SUSPENSION in children below the age of 12 months have not been established.

ADVERSE REACTIONS: The most frequent type of adverse reaction occurring with CHILDREN'S ADVIL® SUSPENSION is gastrointestinal. In clinical trials among adults involving chronic administration of ibuprofen, the percentage of patients reporting one or more gastrointestinal complaints ranged from 4% to 16%.

Incidence Greater Than 1% (but less than 3%), Probable Causal Relationship (see PRECAUTIONS): Abdominal cramps or pain, abdominal distress, constipation, diarrhea, epigastric pain,* fullness of the GI tract (bloating and flatulence), heartburn,* indigestion, nausea,* nausea and vomiting; dizziness,* headache, nervousness; pruritus, rash* (including maculopapular type); tinnitus; decreased appetite; edema, fluid retention (generally responds promptly to drug discontinuation).

Precise Incidence Unknown (but less than 1%), Probable Causal Relationship (see PRECAUTIONS): Abnormal liver function tests, gastric or duodenal ulcer with bleeding and/or perforation, gastritis, gastrointestinal hemorrhage, hepatitis, jaundice, melena, pancreatitis; alopecia, erythema multiforme, Stevens-Johnson syndrome, urticaria, vesiculobullous eruptions; aseptic meningitis with fever and coma, confusion, depression, emotional lability, insomnia, somnolence; amblyopia (blurred and/or diminished vision, scotomata and/or changes in color vision), hearing loss; agranulocytosis, aplastic anemia, decreases in hemoglobin and hematocrit, eosinophilia, hemolytic anemia (sometimes Coombs' positive), neutropenia, thrombocytopenia with or without purpura; congestive heart failure in patients with marginal cardiac function, elevated blood pressure, palpitations; anaphylaxis, bronchospasm (see CONTRAINDICATIONS), syndrome of abdominal pain, fever, chills, nausea and vomiting; acute renal failure in patients with pre-existing significantly impaired renal function, azotemia, cystitis, decreased creatinine clearance, hematuria, polyuria; dry eyes and mouth, gingival ulcers, rhinitis.

Precise Incidence Unknown (but less than 1%), Causal Relationship Unknown: Dream abnormalities, hallucinations, paresthesias, pseudotumor cerebri; photoallergic skin reactions, toxic epidermal necrolysis; cataracts, conjunctivitis, diplopia, optic neuritis; bleeding episodes (e.g., epistaxis, menorrhagia); acidosis, gynecomastia, hypoglycemic reactions; arrhythmias (sinus tachycardia, sinus bradycardia); angioedema, Henoch-Schönlein vasculitis, lupus erythematosus syndrome, serum sickness; renal papillary necrosis.

*Reactions occurring in 3% to 9% of adult patients treated with ibuprofen.

OVERDOSAGE: Patients with a history of ingestion of greater than 100 mg/kg should have induced emesis or gastric lavage. Multiple dose oral administration of activated charcoal may be useful. Supportive therapy may include oxygen, respiratory support, and parenteral fluids. Because the drug is acidic and excreted in the urine, administration of sodium bicarbonate and induction of diuresis may be beneficial.

DOSAGE AND ADMINISTRATION: Fever: 5 mg/kg if baseline temperature is 102.5°F or below or 10 mg/kg if baseline temperature is greater than 102.5°F, every 6-8 hours (children); 400 mg every 4-6 hours (adults).

Mild to moderate pain in adults: 400 mg every 4 to 6 hours.
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RA and OA: 1200-3200 mg per day in 3 or 4 divided doses.
Dysmenorrhea: 400 mg every 4 hours.

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Detection of Alcoholism in Hospitalized Children and Their Families

Anne K. Duggan, ScD; Hoover Adger, Jr, MD, MPH; Eileen M. McDonald;
Emma J. Stokes, PhD; Richard Moore, MD, MHS

• The study sought to measure provider recognition of family alcohol-related problems among hospitalized children and to identify characteristics distinguishing "positive" families. The study sample (N = 147) was drawn from admissions to the general pediatric medical service of a metropolitan teaching hospital. Positivity was assessed through parent and patient interviews that included standard alcohol abuse screening instruments. Provider recognition was assessed through record review and physician interview. Of the 22 families screened positive, only one was so identified by the child's attending or resident physician. Positive and "negative" families were similar in most respects, although parents in positive families were more likely to report stress and sleeping problems and adolescents were more likely to report being troubled by a parent's drinking. The similarity of positive and negative families and the low pediatrician recognition rate suggest that alcohol problems are likely to go unnoticed without a conscious screening effort.

(*AJDC.* 1991;145:613-617)

The importance of substance abuse as a pediatric health care problem stems from its high prevalence among patients and their families, its unfavorable and serious consequences, and the effectiveness of timely recognition and treatment. More than 15 million Americans are estimated to meet the *Diagnostic and Statistical Manual of Mental Disorders, Third Edition,* criteria for alcohol abuse or dependence,[1] and about one in eight American children has a parent with a past or present drinking problem.[2]

For editorial comment see p 609.

Adverse consequences of this disease extend beyond the alcoholic to his or her family. For children in an alcoholic household, home life is chaotic and emotionally unsupportive.[3] In the short run, such an environment erodes the child's physical and emotional well-being.[4] In homes where alcoholism remains undetected and untreated, consequences extending to adulthood include low self-esteem, inability to trust, difficulty in expressing anger appropriately, and a distorted sense of the extent and limits of one's responsibilities.[5]

Adult substance abuse often begins in adolescence. Among high school seniors nationally, use in the past month was reported by 64% for alcohol and 18% for marijuana.[6] Substance abuse can adversely affect the adolescent's physical, mental, and emotional health. Alcohol use is related to 40% of accidental deaths, 30% of homicides, and 20% of suicides among adolescents.[7] Cognitive and psychosocial consequences include developmental lag, amotivational syndrome, escapism, egocentrism, self-deprecation, and alienation.[8]

Pediatricians are in a unique position to identify and respond to substance abuse among patients and their families. Even so, because substance abuse is given low priority in pediatric medical education, pediatricians are ill equipped to identify and respond to substance abuse in patients and their families.[9] Potential barriers to detection and response are varied, and they relate to the individual provider, his or her medical training, and characteristics of the disease. The pediatrician may not perceive his or her role as extending to the patient's family. Medical training in all but the end stages of the disease of alcoholism and drug addiction may be inadequate. The provider may be unaware of available treatment resources or may question the effectiveness of treatment. Even those who are motivated and knowledgeable may lack the interviewing skills necessary to break through patient and family denial of alcoholism and other drug dependence.

As part of a larger institutional effort to develop a comprehensive approach to drug and alcohol education, a baseline survey of the prevalence and provider recognition of alcoholism among hospital inpatients was conducted. An earlier article describes the methods and findings for the departments of internal medicine, obstetrics and gynecology, surgery, and psychiatry.[10] This article focuses on the department of pediatrics, for which the survey assessed alcohol abuse prevalence and provider recognition not only among patients but also among their parents and other primary caregivers. Families screened "positive" are compared with those screened "negative" in terms of demographic, health, and behavioral characteristics.

PATIENTS AND METHODS

The study population was defined as children and adolescents admitted to the general pediatric medical service of The Johns

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Accepted for publication December 13, 1990.

From the Departments of Pediatrics (Drs Duggan and Adger and Ms McDonald) and Medicine (Dr Moore), and the Blades Center for Clinical Practice and Research in Alcoholism (Dr Stokes), The Johns Hopkins University School of Medicine,Baltimore, Md.

Reprint requests to Department of Pediatrics, Park 307, The Johns Hopkins Hospital, 600 N Wolfe St, Baltimore, MD 21205 (Dr Adger).

Hopkins Children's Center, Baltimore, Md. The study sample was drawn from all such hospital admissions from August 1987 to November 1987. Signed informed consent was obtained for participating parents and children aged 10 years or older. As mandated by the institutional review board, patients judged by the unit nurse as too sick to be interviewed and those with a new diagnosis of cancer were excluded.

Prevalence data were collected by trained interviewers through structured interviews with the parent and with patients older than 9 years. Priority was given to interviewing the mother but, where this was impossible, the father or grandmother was interviewed. Data on provider recognition of substance abuse problems were collected through record review and through interviews with the house officer and attending physician for each family that screened positive and for a sample of those who had screened negative on parent or child interview.

The parent interview solicited information on family demographics, parent health status, and health-related behaviors. When the child was younger than 10 years, the parent interview included the Child Behavior Checklist[11] to measure parent-reported behavior.

The parent's use of alcohol was assessed in terms of quantity-frequency and by responses to the brief version of the Michigan Alcohol Screening Test (Brief MAST)[12,13] and the CAGE (which is explained below).[14] Alcohol use by the child's other parent, including both a surrogate parent living in the home and a biological father whether in or out of the child's home, was also ascertained. This was accomplished by administering the Brief MAST and CAGE to the participating parent as a proxy respondent for the other parent.[15]

The Brief MAST is a set of 10 questions concerning alcohol use and associated consequences. The questions are weighted, and a score is derived as the weighted sum of answers suggestive of alcohol-related problems. The CAGE is a screening framework whose name is derived from the first letters of four areas of questioning about the subject's or another's drinking: *C*oncern over alcohol use, *A*nnoyance with another's suggestion to alter use, *G*uilt over behavior while intoxicated, and need for an *E*ye-opener drink to start the day. The CAGE score is the number of these four areas in which the subject replies in the affirmative.

The interview for older children and adolescents included questions on family composition, the child's health care utilization and health habits, indicators of health status, and use of cigarettes and alcohol and other drugs. Alcohol use was measured in terms of quantity-frequency, the Adolescent Alcohol Involvement Scale (AAIS),[16] and the CAGE. The adolescent's reasons for drinking were measured by the Perceived Benefits of Drinking Scale.[17] Experience with each of several classes of drugs was measured as never used/nonregular use/regular use. Finally, the adolescent was asked whether he or she had ever been troubled by the drinking of a parent or caregiver.[18]

A Brief MAST score of 6 or greater was considered positive for alcoholism; two or more affirmative responses to the four CAGE items was also considered positive. For the AAIS scale, a score of 42 or greater indicated positivity. A family was considered positive for alcohol abuse if the Brief MAST or CAGE score for a biological parent or surrogate parent in the household was positive or if the CAGE or AAIS score was positive for an adolescent patient.

For all families who screened positive and a random 15% sample of those who screened negative for alcohol abuse, data on provider recognition of and response to alcoholism were collected through record review and interviews with the resident and attending physicians. Documented assessment of substance use by both the patient and family was determined through record review. The provider interviews determined whether the provider had identified substance use in the patient or a family member, the means of identification, and the treatment given. The statistical significance of differences between positive and negative families was assessed using Student's *t* test and χ^2.

RESULTS

There were 246 general pediatric medical admissions to the hospital during the study period. Of these, 19 children (8%) were judged by the unit nurse to be too sick to participate in the study. Of the remaining 227 children, 27 parents (12%) refused participation, and no parent or caregiver was available for interview in 53 instances (23%). Parents of 147 children (65%) agreed to participate in the study. Of the 147 admitted children in participating families, 82 were 10 years or older. Of these, 59 (72%) were interviewed, nine (11%) were unavailable for interview during times of interviewer coverage, and 14 (17%) refused to be interviewed.

Table 1.—Comparison of Parents by Household Screening Status

Characteristics of Parent Interviewed	Total, % (n=147)	Household Screening Status, %		P
		Positive (n=22)	Negative (n=125)	
Age, y*	35.7±6.2	36.0±5.1	35.7±6.6	.83
Sex, F	99	100	98	1.00
Race, W	76	73	77	.89
Employed	59	68	57	.44
Income <$20 000	30	46	27	.15
Education				.87
<High school	15	18	15	. . .
High school and some college	62	64	62	. . .
≥College graduate	22	18	23	. . .
Gets adequate sleep seldom or never	25	41	22	.11
Has insomnia usually/always	17	32	14	.07
Has had stress frequently/constantly in past year	36	54	30	.04
Depressed for period of >2 wk in past year	28	41	26	.25
Perceives own health as				.34
Excellent	32	18	34	. . .
Good	54	64	52	. . .
Fair or poor	15	18	14	. . .
Smokes	43	54	41	.33
Perceives patient's health as				.06
Excellent	30	27	30	. . .
Good	48	32	51	. . .
Fair or poor	22	41	19	. . .

*Values are means ± SDs.

In 22 (15%) of the 147 participating families, either a parent or child was determined to be positive for alcoholism. Screen-positive family members included four primary female caretakers, eight biological or surrogate fathers inside the household, nine biological fathers living outside the household, and one adolescent patient. In 15 of the 22 positive households, the patient was aged 10 years or older, and in seven positive households the patient was younger than 10 years.

Provider recognition of alcoholism was poor. Of the 22 families screened positive by parent or adolescent interview, only one was identified as such by the attending physician; none were identified by house officers. Two of the families screened negative in the study were identified as having a family history of alcoholism by the resident or attending physician.

Table 2.—Comparison of Adolescents by Household Screening Status

		Household Screening Status, %		
Adolescent Characteristics	Total, % (n=59)	Positive (n=10)	Negative (n=49)	P
Age, y*	14.6±2.7	14.6±2.4	14.6±2.8	.99
Race, B	22	20	23	1.00
Sex, M	49	60	47	.68
Sees dentist annually	75	80	74	.97
Has annual medical checkup	61	50	63	.67
Eats balanced meals daily	76	78	76	1.00
Exercises ≥3 times weekly	66	60	67	.94
Gets adequate sleep seldom/never	20	30	18	.69
Has insomnia most every night	15	20	14	1.00
Depressed for a period of ≥2 wk in past year	39	50	37	.69
Has headaches, stomachaches, or other recurrent problems	75	80	74	.97
Discusses problems with no one	16	10	17	.96
Not active in extracurricular activities	50	30	54	.30
Has been troubled by a parent's drinking	5	23	2	<.001
Has used drugs	5	20	2	.07
Does drink alcohol	8	10	8	1.00

*Values are means ± SDs.

Positive and negative families were similar for most of the demographic parent characteristics examined (Table 1). The interviewed parents were 36 years old on average, almost all were female, and three quarters were white. About three fifths of the interviewed parents were employed. Differences in household income approached significance ($P = .15$); 46% of those in positive households as compared with 27% of those in negative households reported an income of less than $20 000. Parents did not differ in terms of educational status, with less than a fifth in each group lacking a high school diploma.

Parents in positive households were less likely to report routinely getting adequate sleep ($P = .11$), and they were more likely to report frequent insomnia ($P = .07$) and frequent or constant stress in the past year ($P = .04$). Group differences in the proportion reporting depression for more than 2 weeks were similar but less pronounced (positive households 41% vs negative households 26%, $P = .25$). Positivity was not related to parent smoking or to the parent's perception of his or her own health status. Parents in positive households were more likely to characterize their child's health as only fair or poor (41% vs 19%, $P = .06$).

Table 3.—Differences in Child Behavior* by Household Screening Status

	Household		
Child Behavior Score	Positive (n=7)	Negative† (n=14)	P
Activity	35.1	47.3	.14
Social	43.5	44.6	.79
T			
Sum	51.4	52.5	.83
Internal	55.4	51.1	.35
External	46.9	50.2	.52

*As measured by parental report using the Achenbach Child Behavior Checklist.[11]

†Each subject younger than 10 years old in positive households was matched on age, sex, and race with two controls from negative households.

Among adolescent patients, household positivity for alcoholism was not related to patient age (mean, 14.6 years), race (22% black), or sex (49% male) (Table 2). Most adolescents in both positive and negative households reported good health practices: 61% of the adolescents had annual medical checkups; 75% had annual dental checkups; 76% ate balanced meals daily; and 66% exercised at least three times weekly.

The likelihood of health-related problems did not differ significantly between adolescents in positive and negative families. Sleep problems were fairly common: 20% seldom or never got adequate sleep; 15% indicated they had insomnia most nights. Two-fifths reported feeling depressed 2 weeks or more in the past year. Headaches, stomachaches, or other recurrent problems were the norm and were reported by 75% of the adolescents. About one in six adolescents reported having no one with whom to discuss problems. Half of the adolescents were not involved in extracurricular activities at school.

The groups differed markedly in their reaction to parental drinking. Those in positive households were much more likely to indicate they had been troubled, scared, or angry because of a parent's drinking (23% in positive households vs 2% in negative households, $P < .001$).

Group differences in reported prior use of drugs approached significance (20% of those in positive households vs 2% in negative, $P = .07$). The three patients with prior drug use all reported using marijuana. In addition, the adolescent who screened positive for alcohol use also reported having used amphetamines and lysergic acid diethylanmide.

Five adolescents (8%) reported current alcohol use. One adolescent screened positive on the CAGE, although not on the AAIS, where scores ranged from 24 to 41. When queried about the perceived benefits of drinking, one of the five adolescents reported that drinking helped him be friendly, and two adolescents, including the adolescent who screened positive, reported it helped them relax. None of the five adolescents reported drinking as a means to help forget problems, feel good about oneself, or be friends with others who drink.

Table 3 summarizes parental assessment of behavior for patients younger than 10 years by household positivity. Each of the seven children from positive households was matched by age and sex with two controls from negative households. Children in positive and negative households did not differ significantly on any behavior subscore and had behavior scores within group norms.

COMMENT

The 15% prevalence rate of positive screens for alcoholism in hospitalized pediatric patients and their parents was consistent with national estimates of the lifetime prevalence of alcoholism and alcohol abuse (11.5% to 15.7%)[19] and somewhat lower than rates found for adult inpatients in most other departments of our institution: psychiatry (30%); medicine (25%); surgery (23%); neurology (19%); and obstetrics-gynecology (12.5%).

There are several reasons to suspect that the 15% prevalence rate is conservative. First, anecdotal evidence suggested that positive families were more likely to decline study participation. Many families were known to nursing staff from prior hospitalizations. At least a few parents who refused to be interviewed or who judged their child too sick to participate were believed by nursing staff to be from alcohol-dependent families. Second, parent interviewing was limited to the inpatient setting. To the extent that family alcoholism negatively influenced hospital visiting, parents in positive households were less likely to be recruited for participation. Third, insofar as alcoholism was viewed by parents as socially unacceptable behavior, there was motivation for underreporting by those interviewed. A final reason pertains to the interviewed parent's role as proxy respondent for the Brief MAST and CAGE items relating to the other parent. To the extent that the interviewed parent could not or would not answer items, the likelihood of a positive screen for the other parent was decreased.

Screen positivity for alcoholism was not a problem limited to any particular patient subgroup. Both parents and patients in positive and negative families were similar in most respects. Parents in positive households were more likely to suffer from stress and sleep problems, and adolescents were more likely to be troubled by a parent's drinking. Given the small sample sizes, only substantial group differences could attain statistical significance. From the perspective of teaching pediatricians how to identify families with alcohol-related problems, the similarities between positive and negative families are perhaps more important. The similarities demonstrate the lack of sensitivity of typical substance abuse stereotypes—unemployment, low income, lack of education—as a way of identifying families with problems.

Provider recognition of families who screened positive was low. Only one of the positive families was identified as such by the physician. In this family, both parents had a positive history, the child had been removed from home for a time, one parent had been in treatment in the past, and the provider reported not knowing the parents' current state of recovery. The adolescent patient who screened positive for alcohol use also reported past use of marijuana, amphetamines, and lysergic acid diethylamide. This patient was not recognized as positive by either the attending or resident physician.

Provider recognition rates were substantially lower in pediatrics than in most other departments. Only one (5%) of the positive families was so identified by a pediatric attending physician as compared with 27% of positive cases detected by attending physicians in neurology and in surgery, 35% in medicine, and 65% in psychiatry. While pediatric house officers detected none of the screen-positive families, house staff recognition rates in other departments were 20% in surgery, 46% in neurology, 52% in medicine, and 66% in psychiatry. As in pediatrics, attending physicians in obstetrics-gynecology recognized only 7% of positive cases and house officers recognized none.

No doubt the pediatric recognition rate was lower because positivity was defined to include parents as well a patients and because many pediatricians did not view thei role as extending to family members. This attitude wa demonstrated in a 1988 survey of our pediatric faculty and house staff.[20] Faculty were twice as likely to feel little o no responsibility for substance abuse referral of patien family members as compared with adolescent patients (33% vs 15%). This trend was even more pronounced for house staff, of whom 25% and 3% reported feeling little or no responsibility for referral of patient family members as compared with adolescent patients.

The low provider recognition rate of this study is congruent with reported practice behavior. In the 1988 survey cited above, 62% of faculty and house staff reported taking a personal alcohol/drug use history from most or all of their adolescent patients. However, only 34% reported taking a family substance abuse history for their pediatric patients.

Some may question whether it is appropriate to expect physicians providing inpatient care to identify patient and family alcohol problems. Certainly, a family history of alcohol and drug abuse is more likely than many other aspects of history to affect a patient's immediate and follow-up treatment. Family problems with alcohol and other drugs can jeopardize a parent's ability to carry out necessary therapeutic regimens. A thorough history, including family and social histories, is required for all patients admitted to the hospital. We believe personal and family histories for substance abuse are just as important as a history for hypertension, cancer, or diabetes mellitus.

The generalizability of findings is limited by study of an inpatient population rather than a primary care setting. The inpatient setting was chosen because it was suspected to have the lowest provider recognition rate and the greatest provider resistance to patient and family substance abuse screening. Certainly, replication of this study in primary care settings serving both general populations and children with chronic conditions would provide much needed information on the prevalence and pediatrician identification and management of family substance abuse problems.

CONCLUSION

This study was undertaken to assess the prevalence of patient and family positivity for alcoholism in an inpatient pediatric setting and to describe provider behavior in dealing with identified families. We found that family alcoholism was distributed in this population as it is distributed more generally, across all socioeconomic and demographic strata. We conclude from this that if alcohol-dependent families of pediatric patients are to be identified, all families must be screened.

We also found that pediatricians in our setting failed to recognize most alcohol-dependent families. We conclude from this that in many instances, family alcoholism is not likely to be a blatant problem, but rather one whose identification requires a deliberate and skilled screening effort. If pediatricians are to make family screening for substance abuse a routine part of care, they must learn how to screen and they must be convinced of the importance of doing so. Macdonald and Blume[3] have well described the importance of family screening and have suggested the utility of the CAGE framework as a means for detecting alcohol abuse.

What might pediatricians do with increased awareness of parental drinking problems? It is important for the pediatrician to remember that a positive screen does not make a diagnosis. As Macdonald and Blume[3] point out, a diagnosis of alcoholism is often difficult for a parent to accept. A diagnosis that is reached too hastily and without a complete and thorough assessment may sever the physician-family relationship rather than strengthen it. The pediatrician should advocate further exploration into the area, either with himself or herself or with an assessment specialist. It is important for the pediatrician to express his or her concern for the parent and child and the belief that alcoholism is not a moral weakness but a treatable disease. In addition, the pediatrician can play an important role in educating the family and can help the parent to explore the links between parental drinking and family dysfunction. The pediatrician can offer the parent referral to a substance abuse counselor or support group as a means for learning more about whether there is a problem with family alcoholism, and if so, how to deal with it. In this spirit, the parent is more likely to interpret the pediatrician's actions as genuine concern and to respond in a positive manner.

In our institution, the results of this study and related research are being used to help motivate pediatricians to incorporate substance abuse identification and initial management in their practice. Essential aspects of this effort include the teaching of clinical screening skills, including the CAGE framework, reinforcing the role of the physician in early detection and minimal interventions, and disseminating information on the availability of institutional and community treatment resources. Our experience suggests that assessing prevalence and practice is a useful first step for improving physician recognition and response to substance abuse.

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In Other AMA Journals

ARCHIVES OF OTOLARYNGOLOGY—HEAD & NECK SURGERY

Balloon Dilatation of Esophageal Strictures in Children

Charles M. Myer III, MD; William S. Ball Jr, MD; George S. Bissett III, MD
(*Arch Otolaryngol Head Neck Surg*. 1991;117:529-532)

Article

The Causes of Hospital-Treated Acute Lower Respiratory Tract Infection in Children

Hanna Nohynek, MD; Juhani Eskola, MD; Eija Laine, MD; Pekka Halonen, MD; Petri Ruutu, MD; Pekka Saikku, MD; Marjaana Kleemola, MD; Maija Leinonen, PhD

• ***Objective:*** **To determine the etiologic agents in children with acute lower respiratory infection.**

Design: **A survey of a series of patients.**

Setting: **General pediatric hospital serving an urban population with and without referrals in Helsinki, Finland.**

Participants: **135 Finnish children aged 2 months to 15 years (mean, 1.75 years), with clinically defined acute lower respiratory infection (with difficulty of breathing), or found to have fever and a pneumonic infiltrate on chest roentgenogram.**

Selection Procedures: **Consecutive sample on voluntary basis.**

Interventions: **None.**

Main Results: **Of 121 children with adequate samples, an etiologic diagnosis could be established in 84 (70%): 30 (25%) had bacterial, 30 (25%) viral, and 24 (20%) mixed infections. Antibody assays alone identified the agent in 91% of positive cases.**

Conclusions: **Bacterial infections are common but generally underestimated in acute lower respiratory infection; serologic methods add significantly to their detection.**

(*AJDC.* 1991;145:618-622)

Acute lower respiratory tract infection (ALRI), ie, pneumonia and bronchiolitis, is a major cause of morbidity among children worldwide.[1] In addition, these diseases cause significant mortality in the developing countries.[1-3] The causes of ALRI are still partly unknown, primarily because of difficulties in obtaining adequate samples and lack of reliable diagnostic methods.[4,5] This is a major shortcoming, since knowledge of the etiologic agents of ALRI in different patient populations would be of crucial importance for both development of vaccines and recommendations regarding treatment.

We report here a study of 121 urban Finnish children hospitalized because of clinically defined ALRI. We used both conventional microbiological methods and a broad range of serologic methods, including bacterial antibody assays and detection of viral and bacterial antigens and nucleic acid, which allowed us to find the presumptive cause of ALRI in 70% of the patients.

PATIENTS AND METHODS

The study was carried out from December 1987 to November 1988 in Aurora Hospital, Helsinki, Finland, with the permission of its Ethics Committee. The hospital serves an urban population with and without referrals. Informed consent was obtained from the parents in each case.

Patients

All children aged 15 years or younger hospitalized for respiratory infection were enrolled in the study if they fulfilled the following criteria judged by the pediatrician on duty: symptoms of acute respiratory infection lasting 7 days or less, together with difficulty of breathing defined as chest indrawing or respiratory rate of more than 40/min for infants or more than 30/min for those older than 1 year. In addition, children hospitalized for other reasons but found to have fever (≥38°C) and a pneumonic infiltrate on chest roentgenogram were included in the study.

Specimens

Nasopharyngeal aspirates (NPAs) of respiratory secretions and urine were collected on admission. Blood was collected on admission, on days 3 and 5, and during convalescent checkup examination (day 36 on the average; range, 14 to 96 days).

Blood Culture

One to five milliliters of venous blood taken on admission was cultured using standard techniques (Bactec NR 660, Becton Dickinson Diagnostics Instruments Systems, Towson, Md).

Bacterial Antigen Detection

The urine samples were tested for capsular polysaccharide of *Haemophilus influenzae* type b and for pneumococcal polysaccharides of the most common serotypes reported in Finnish children (types 4-9, 11, 14, 15, 19, and 23) (M.L., unpublished observations, 1988) by type-specific latex reagents made from monospecific antiserum (for *H influenzae* type b: burro 46, provided by John B. Robbins, MD, National Institutes of Health, Bethesda, Md; for *Streptococcus pneumoniae* serotypes: Statens Seruminstitut, Copenhagen, Denmark) as described.[6] The serum samples obtained on admission were tested with a commercial latex agglutination test (Bactigen, Wampole Laboratories, Cranbury, NJ) for pneumococcal capsular polysaccharide antigens.

Mycoplasmal RNA Hybridization

Homogenized NPA was used for detection of nucleic acid of *Mycoplasma pneumoniae* by RNA hybridization as specified by the producer of the kit (Gen-Probe Rapid Diagnostic System, San Diego, Calif).

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From the National Public Health Institute, Helsinki, Finland (Drs Nohynek, Eskola, Kleemola, and Leinonen); Aurora Hospital, Helsinki (Drs Eskola and Laine); Second Department of Medicine, Helsinki University Central Hospital (Dr Ruutu); and the Departments of Virology, Universities of Helsinki (Dr Saikku) and Turku (Finland) (Dr Halonen).

Reprint requests to National Public Health Institute, Mannerheimintie 166, SF-00300 Helsinki, Finland (Dr Eskola).

Table 1.—Methods Used to Measure Antibodies to the Common Respiratory Pathogens Studied*

Agent	Antigen Used	Antibody Class	Method	Significant Response	Source, y
S pneumoniae	Pneumolysin	IgG	EIA	2-fold† increase in titer	Jalonen et al,[11] 1989
H influenzae	Whole cell‡	IgG, IgA	EIA	3-fold† increase in titer	Leinonen et al,[12] 1981
M catarrhalis	Whole cell‡	IgG, IgA	EIA	3-fold† increase in titer	Leinonen et al,[12] 1981
M pneumoniae	Whole cell§	IgG, IgM	EIA	3-fold increase in titer	Kleemola et al,[13] 1990
C pneumoniae, *C psittaci,* *C trachomatis*	Type-specific elementary bodies‖	IgG, IgM	mIF	4-fold increase in titer or presence of IgM	Wang et al,[14] 1970
Respiratory syncytial virus	Cell-lysed viruses	IgG	EIA	4-fold increase in titer	Meurman et al,[15] 1984
Influenza A or B	AFP	IgG	EIA	3-fold increase in unit value	Koskinen et al,[16] 1987
Parainfluenza types 1, 2, or 3	1, AFP; 2, 3, CL	IgG	EIA	3-fold increase in unit value	Vuorinen et al,[17] 1989
Adenovirus	Group-reacting hexon	IgG	EIA	3-fold increase in unit value	Meurman et al,[18] 1983

*EIA indicates enzyme immunoassay; mIF, microimmunofluorescence; and AFP, allantoic fluid-pelleted viruses. Full expansion of names of agents appears in the text.

†Based on measurements of antibodies in paired serum samples from 158 healthy children (M.L., unpublished observations).

‡Whole bacterial cell suspension of 10 different strains.

§*Mycoplasma pneumoniae* organisms lysed by 2% sodium dodecylsulfate.

‖Following elementary bodies were used: *C trachomatis,* A, C-H-I-J, K-G-F, B-D-E; *C pneumoniae,* AR-39; and *C psittaci,* V-394.

Viral Antigen Detection

Sonicated NPA diluted 1:5 in assay buffer was used for detection of respiratory syncytial virus (RSV), group-reacting hexon antigen of adenoviruses, influenza A and B, and parainfluenza types 1, 2, and 3 antigens by one-incubation time-resolved fluoroimmunoassay based on immunoreagents prepared from monoclonal antibodies.[7-10]

Antibody Assays

The methods and diagnostic criteria used in antibody assays are listed in Table 1.[11-18] Serum samples were tested for antibodies to *S pneumoniae, H influenzae, Moraxella (Branhamella) catarrhalis, M pneumoniae, Chlamydia trachomatis, Chlamydia psittaci,* and *Chlamydia pneumoniae,* and for antibodies to RSV and adenovirus, influenza A and B, and parainfluenza types 1, 2, and 3.

Criteria for Etiology

The infection was considered bacterial if at least one of the following criteria was fulfilled: a positive blood culture, a significant bacterial antibody response, or positive antigen detection in serum or urine. For *M pneumoniae,* a positive RNA hybridization test result in NPA was also considered indicative of infection. Viral infection was defined as a positive antigen finding in NPA or a significant antibody response. Mixed infection was defined as a concomitant finding of a bacterial and viral agent. If two or more bacterial or viral agents were found, the infection was considered to be a bacterial or viral coinfection, respectively.

Statistical Methods

The χ^2 test with Yates' correction or Fisher's Exact Test, when appropriate, were used to test the differences in distributions of the etiologic agents. The Wilcoxon rank sum test was used to analyze the differences in clinical and laboratory variables indicative of infection.

Table 2.—Comparison of Assays Detecting Microbial Antigen (or RNA) With Those Detecting the Antibody Response

	Combination of Findings*			
Pathogen†	Ab+/Ag−	Ab+/Ag+	Ab−/Ag+	Total
S pneumoniae	15	0	4‡	**19**
H influenzae type b	0	1	1	**2**
M pneumoniae	4	4	3	**11**
Respiratory syncytial virus	12	19	3	**34**
Adenovirus	11	4	1	**16**
Parainfluenza 1, 2, or 3	7	1	0	**8**
Influenza A or B	2	2	0	**4**
Total	**51**	**31**	**12**	**94**

*Ab indicates significant antibody response; Ag, antigen or RNA (for *M pneumoniae*) detection; plus sign, positive finding; and minus sign, negative finding.

†Full expansion of names of pathogens appears in the text.

‡One case with a positive blood culture.

RESULTS

A total of 135 patients were enrolled during the 1-year study period. Fourteen patients lacked paired serum samples and were excluded from the etiologic part of the study; they did not differ from the rest of the patients in age, clinical signs and symptoms or laboratory indexes, erythrocyte sedimentation rate, white blood cell count, and C-reactive protein level.

The median age of the remaining 121 children was 1.75 years (range, 4 months to 15 years). Fifty-nine percent were male and 41% female. The majority (n = 108) were enrolled on the basis of clinical criteria of ALRI, and 13 on the basis of fever and chest roentgenographic findings. Of the 108 patients enrolled on clinical criteria, a pneumonic infiltrate was found in 80%. Acute otitis media, defined as

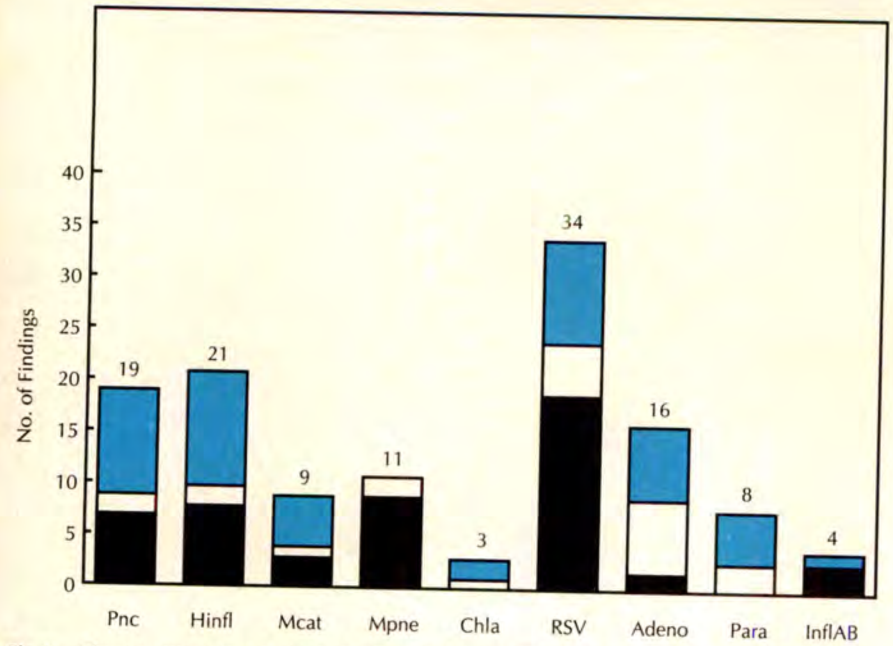

Fig 1.—*The presumptive etiologic findings in 121 children with acute lower respiratory infection based on blood culture, measurement of antibodies, and detection of antigen or RNA. Pnc indicates* Streptococcus pneumoniae; *Hinfl,* Haemophilus influenzae; *Mcat,* Moraxella catarrhalis; *Mpne,* Mycoplasma pneumoniae; *Chla,* Chlamydia *species; RSV, respiratory syncytial virus; Adeno, adenovirus; Para, parainfluenza viruses types 1, 2, and 3; and InflAB, influenza A and B viruses. Closed bars represent a single finding; open bars, two or more bacterial findings together, or two or more viral findings together; and tinted bars, one or more bacterial with one or more viral findings.*

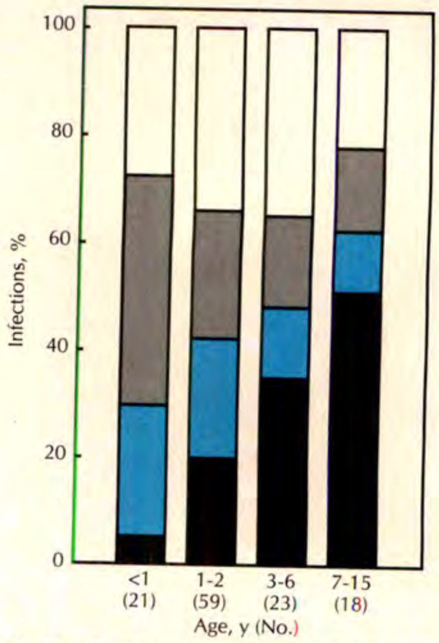

Fig 2.—*Percentages of bacterial (closed bars), mixed (tinted bars), viral (shaded bars), and unknown (open bars) etiologic agents of acute lower respiratory infection in different age groups among 121 children.*

detection of an immobile and inflamed tympanic membrane by pneumatic otoscopy or purulent secretion by myringotomy, was found in 15 of the 96 patients in whom the status of the middle ear was recorded. All children received antimicrobial therapy. The majority of the patients were treated parenterally with procaine penicillin G for 3 to 5 days; 11 patients received other antimicrobial agents (sodium cefuroxime, cefaclor, erythromycin ethylsuccinate, or ampicillin sodium). There were no deaths. All patients recovered without major complications.

Etiologic Diagnosis

Presumptive evidence for the etiologic characteristics of ALRI was detected in 84 (69%) of the 121 patients. Thirty (25%) episodes were found to be associated with a bacterial and 30 (25%) with a viral agent; in 24 (20%), a mixed infection was diagnosed. The methods by which the different etiologic agents were detected are shown in Table 2. Antibody assays alone would have identified the agent in 91% of the positive episodes; antigen detection was less sensitive for most of the microbes (*H influenzae* type b being an exception). Hybridization of RNA identified *M pneumoniae* as often as did antibody assays. The presence of acute otitis media did not increase the etiologic yield; acute otitis media was not associated with any specific etiologic agent or group, or with any one method to implicate the etiologic agent. The finding of a pneumonic infiltrate on chest roentgenogram also did not influence the distribution of causative agents.

Bacterial Agents

Among the bacterial agents (Fig 1), *H influenzae* and *S pneumoniae* were the most common findings, in 17% and 16% of all patients, respectively. *Moraxella catarrhalis* was found in 7% and *M pneumoniae* in 9% of the cases. *Chlamydia* species were found in three patients: *C trachomatis* in two and *C pneumoniae* in one; no *C psittaci* were found. In five patients, two bacterial agents were identified: *S pneumoniae* together with *M pneumoniae* and *H influenzae; H influenzae* with *M pneumoniae* or *M catarrhalis;* and *M catarrhalis* with *C trachomatis.*

Viral Agents

Of the viral agents (Fig 1), RSV was the most common finding, seen in 28% of the patients. The majority of the RSV cases (32 of 34) occurred during a local epidemic in the beginning of the study (December to January). No other seasonal variation was seen among the viral or bacterial agents. The rest of the viral findings were adenovirus in 13%, influenza A or B in 3%, and parainfluenza type 1, 2, or 3 in 7% of the cases. Eight patients had a viral coinfection: RSV together with adenovirus or parainfluenza 1 and 3, and adenovirus with parainfluenza 1 and 3.

Mixed Causes

All bacterial agents except *M pneumoniae* were found with a concomitant viral agent in some patients. Among the viruses, all but influenza B and parainfluenza type 2 were found in association with a concomitant bacterial agent. There was no specific association between a certain bacterium and a certain virus. The proportions of mixed findings among the different agents are shown in Fig 1.

Etiologic Characteristics and Age

The relationship between the different etiologic groups and the age of the patient is shown in Fig 2. The proportion of bacterial ALRI steadily increased with age, whereas the proportion of mixed and pure viral ALRI decreased. *Streptococcus pneumoniae* was seen in all ages and *M pneumoniae* in all ages except for infants; the proportional roles of both

Table 3.—The Relation Between the Age of the Patient and the Etiologic Agent*

Etiologic Agent	No. (%) of Findings by Age Group, y <2 (n=66)	≥2 (n=55)	P
S pneumoniae	6 (9)	13 (24)	<.03
H influenzae	13 (19)	8 (14)	NS
B catarrhalis	5 (7)	4 (7)	NS
M pneumoniae	2 (3)	9 (16)	<.01
Chlamydiae	2 (3)	1 (2)	NS
Respiratory syncytial virus	26 (38)	8 (14)	<.003
Adenovirus	12 (17)	4 (7)	NS
Parainfluenza	3 (4)	5 (9)	NS
Influenza A or B	0 (0)	4 (7)	NS
Total	**69**	**56**	. . .
No findings	20	17	. . .

*NS indicates not significant. Full expansion of names of agents appears in the text.

increased with age (Table 3). Respiratory syncytial virus, adenovirus, and *H influenzae* were more common in the younger children; the difference was statistically significant ($P<.003$) for RSV only.

COMMENT

Several problems are faced in establishing the etiologic diagnosis of bacterial ALRI. Blood culture, the "gold standard" of diagnosis, is specific, but insensitive in children with bacterial ALRIs of which less than 10% are bacteremic.[19,20] Invasive methods such as transtracheal aspiration, bronchoalveolar lavage, and lung puncture can seldom be considered justified in pediatric practice, and nasopharyngeal samples provide little etiologic information because of high carriage rates of the potential bacterial pathogens.[21,22] Methods to detect antigens in serum and urine are available, but both their specificity and sensitivity have, until recently, been unsatisfactory.[5,6,20]

Demonstration of a serum antibody response is a well-established indication of viral infection. Antibody assays to detect *S pneumoniae*, nontypable *H influenzae*, and *M catarrhalis* have recently been used in several studies of adult pneumonia,[23,24] demonstrating that bacteria play a significant etiologic role. These new enzyme immunoassays have also been validated in children as follows: when paired serum samples from 158 healthy children less than 14 years old (range, 3 months to 13 years) were studied, no significant responses were found to *M catarrhalis*, and responses to *H influenzae* were seen in less than 4% of the children (M.L., unpublished observations, 1989). So far only a few studies have applied these methods to children with ALRI.[25,26] In accordance with the findings in adult patients, these studies have found a larger involvement of the bacterial pathogens than previously estimated in ALRI of children.

An etiologic diagnosis would have been identified in 45% of the cases, and viruses would have appeared dominant in the etiology of ALRI, had we relied on generally used microbiological methods alone. The use of bacterial antibody assays and antigen detection in addition to conventional methods enabled us to find presumptive evidence for the causes of ALRI in 70% of the patients.

The distribution of the bacterial pathogens corresponded to expectation with the exception of the frequently nontypable *H influenzae*. In children less than 3 years of age, *H influenzae* was a more common bacterial agent than *S pneumoniae*, a finding that, to our knowledge, has not been reported previously from the industrialized world. *Moraxella catarrhalis* was also mainly implicated in children less than 3 years of age and in mixed infections. Although both nontypable *H influenzae* and *M catarrhalis* are common findings in acute otitis media[27,28] and have been also reported in pneumonia in children,[4] their role in the pathogenesis of ALRI is still unclear.

The present study began in December 1987 during a major RSV epidemic. The RSV was by far the most common viral finding in this study, and the majority of them occurred in children younger than 3 years. Adenovirus was the next most common viral finding, outnumbering parainfluenza viruses; it was seen mainly in the same age group as RSV.

In this study, the younger children had few bacterial findings; by contrast, the older children had few viral findings. Several factors probably contribute to these differences. The clinical picture of ALRI in the older children may have been severe enough to require hospitalization only if there was bacterial involvement, whereas in the younger children, ALRI, regardless of etiologic characteristics, may have caused symptoms requiring hospital treatment. Viral epidemics, like the RSV epidemic during this study period, usually affect the youngest children, while the older ones, in whom immunity is already developed, are spared.

The etiologic causes remained unknown in 30% of the children despite a broad range of methods used. There are many possible reasons for this. First, the immaturity of the child's immune system may have led to lack of a measurable seroresponse. Second, antibiotic treatment might have been started in such an early phase of the illness that the immune system did not have enough time to respond to detectable limits[29]; this would reduce the detection of both bacterial and mixed, but not viral, infection. Finally, there might have been etiologic agents we did not search for, such as *Staphylococcus aureus*, *Bordetella pertussis*, cytomegalovirus, coronavirus, and, probably most important, rhinoviruses.[30]

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Michael B. Siegel MD; Ralph F. Wetmore, MD;
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Lawrence W. C. Tom, MD
(*Arch Otolaryngol Head Neck Surg.* 1991;117:533-536)

Periorbital Hematoma Secondary to Sinusitis in a Child

George H. Zalzal, MD
(*Arch Otolaryngol Head Neck Surg.* 1991;117:557-559)

Influenza Type A and B Infections in Hospitalized Pediatric Patients

Who Should Be Immunized?

Janet R. Serwint, MD; Ross M. Miller, MD; Barbara M. Korsch, MD

• Medical records of 99 hospitalized pediatric patients whose respiratory viral cultures yielded influenza type A or B during the winter of 1988/1989 were reviewed. We compared the records of patients considered to be at high risk (n = 43) with those of patients considered to be at low risk (n = 56) to determine differences in morbidity and mortality and if vaccination was warranted. Sixty-six percent of high-risk patients had chronic pulmonary disease. Forty-four percent of the high-risk and 11% of the low-risk patients were hospitalized for 14 or more days. Nosocomial influenza infections were identified in 14% of the high-risk and 4% of the low-risk patients. Four of the high-risk patients and only one of the low-risk patients were intubated. Of the three deaths, two occurred in the high-risk group. None of the high-risk patients who experienced significant morbidity had been immunized. We need to immunize high-risk patients, particularly high-risk pulmonary patients.

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According to the recommendations of the Committee on Infectious Diseases in Children,[1,2] children aged 6 months or older in the following high-risk groups should be immunized against influenza: (1) chronic pulmonary disease; (2) hemodynamically significant cardiac disease; (3) patients receiving immunosuppressive therapy; (4) sickle cell disease and other hemoglobinopathies; (5) chronic renal and metabolic diseases; (6) diabetes; (7) symptomatic human immunodeficiency virus infections; and (8) patients receiving long-term aspirin therapy.

Despite these recommendations, only 1% to 7% of high-risk children for whom the vaccine is recommended receive the vaccine.[3] Reasons for such a low rate of immunization may include the following[3]: (1) influenza is not thought to be associated with significant morbidity or mortality in children; and (2) there is uncertainty about which children aged 6 months or older with high-risk conditions really need the vaccine.

Some of this uncertainty may be justified because vaccine recommendations for children are inferred from risk data in adults. Few investigators have studied children considered to be at high risk.[4-8]

Several studies, including those by Brocklebank et al,[9] Liou et al,[10] and Mullooly et al,[11] have examined influenza infections in hospitalized children, but their definitions of high risk and underlying disease were varied and rather broad. Few studies have compared the sequelae from influenza in high-risk patients, as defined by the Committee of Infectious Diseases, with the sequelae in low-risk patients[12,13] or determined which high-risk patients are most affected by influenza and, thus, would benefit most from immunization.

The purpose of this study was to determine how much morbidity from influenza occurred in high-risk groups for whom the influenza vaccine is recommended compared with low-risk groups, and to determine whether certain high-risk groups are at greater risk for influenza sequelae than other high-risk groups. We hypothesized that high-risk children experience more significant morbidity than low-risk children and that certain high-risk groups are at greater risk of influenza morbidity than other high-risk groups.

MATERIALS AND METHODS

We retrospectively reviewed microbiology records to identify all hospitalized patients from December 1988 through March 1989 with positive influenza A or B respiratory viral cultures. A viral respiratory culture was done on patients hospitalized with a respiratory illness suspected to be of viral cause. The primary reason for obtaining the culture was to diagnose respiratory syncytial virus and to place these patients in contact isolation to avoid nosocomial transmission.

The medical records of these patients were reviewed to identify those who met high-risk criteria. Influenza immunization status was determined by examining hospital charts, influenza immunization lists from subspecialty and primary care clinics, and, when in doubt, contacting the primary care provider. The patients were categorized into high-risk and low-risk groups according to the Committee on Infectious Diseases criteria[1] and were then compared for age at hospitalization and type of influenza yielded. The cutoff age of 6 months was selected for analysis since this is the age at which influenza immunization is recommended. Morbidity from influenza, as measured by length of hospitalization, incidence of intubation, and mortality, was also

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From the Division of General Pediatrics, Department of Pediatrics, Childrens Hospital of Los Angeles, Calif, and the University of Southern California School of Medicine, Los Angeles. Dr Serwint is now with the Division of General Pediatrics, The Johns Hopkins Hospital, Baltimore, Md.

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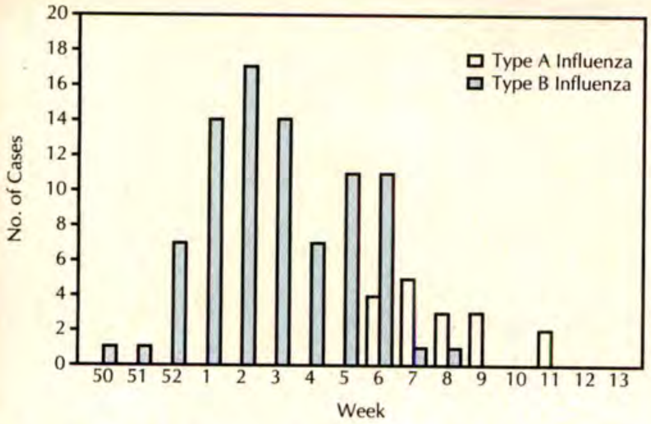

Type of influenza yielded by week.

measured and compared between groups. We identified cases of influenza acquired in nosocomial fashion during hospitalization as another component of morbidity. The high-risk group outcome variables were then divided into subgroups by disease, such as pulmonary and cardiac, to determine if certain high-risk patients experienced more morbidity.

The data were analyzed using χ^2 analysis or Fisher's Exact Test when appropriate.

Specimens from nasopharyngeal swab, endotracheal tube, and tracheostomy suction were first inoculated onto MRC-5 cells (fetal lung tissue), rhesus monkey kidney tissue cells, human foreskin fibroblasts, Hep-2 cells, and A-549 cells (human lung carcinoma). These cells were inoculated at 34°C and observed for cytopathic effect every 3 to 4 days for 2 weeks. Rhesus monkey kidney tissue cell tubes were hemadsorbed with 0.2 mL of 0.5% guinea pig blood cells at 4°C during the first 14 days. Hemadsorption-positive cultures were further evaluated using immunofluorescence staining for influenza A or B virus.

RESULTS

Of 790 viral respiratory cultures obtained from hospitalized patients from December 1988 through March 1989, 112 (14%) were positive for influenza in 99 patients. The hospital records of those 99 patients were reviewed. Their ages ranged from 14 days to 19 years; 53% were male. Of those 99 patients, 43 met the criteria for high risk. In 37 of these high-risk patients and 54 of the low-risk patients, viral cultures were obtained at or shortly after admission. The remaining six high-risk and two low-risk patients were asymptomatic for respiratory symptoms at the time of admission, but cultures for them were obtained 7 or more days after admission when they became symptomatic.

In comparing high-risk and low-risk patients by age, 38 (88%) of the high-risk patients and 21 (38%) of the low-risk patients were aged 6 months or older. This difference was significant at $P<.001$. There was no difference between the high-risk and low-risk groups in type of influenza yielded. Cultures yielded type B influenza more often in both groups (82% of high-risk patients and 80% of low-risk patients). The viral culture from one patient in each group yielded types A and B concomitantly, while the viral culture from an additional high-risk patient yielded influenza B during her first hospitalization and then type A during a second hospitalization, 2½ months later.

We noted that there was an apparent interseasonal distribution in the types of influenza yielded. From December 16 through February 10, cultures yielded only influenza type B except for one case of A in late January. From February 10 through March 15, cultures yielded both types A and B (Figure). The distribution of the high-risk patients by diagnosis according to the criteria established by the Committee of Infectious Diseases is shown in Table 1. The large majority of these patients had pulmonary disease, including patients with asthma, bronchopulmonary dysplasia, congenital emphysema, restrictive lung disease, or chronic aspiration. The other high-risk categories were less well represented in the sample. No patients with diabetes or those receiving long-term aspirin therapy were hospitalized or had culture-positive influenza.

Table 1.—Comparison of High-Risk Patients (n=43) by Diagnosis, Age, and Immunization Status

	Age, mo		
Diagnosis	**<6**	**≥6**	**No. of Patients Immunized**
Pulmonary disease	3	25	4
Cardiac disease	2	3	0
Hemoglobinopathy	0	3	0
Immunosuppression	0	3	0
Immunodeficiency	0	2	0
Renal disease	0	2	0
Total (%) of Patients	**5** (12)	**38** (88)	**4** (11)

Table 2.—Comparison of Morbidity From Influenza Infections Between High- and Low-Risk Patients

	No. (%) of Patients		
Type of Morbidity	**High-Risk (n=43)**	**Low-Risk (n=56)**	***P***
Hospitalization ≥14 d	19 (44)	6 (11)	.001
Nosocomial influenza infection	6 (14)	2 (4)	.05*
Intubation	4 (9)	1 (2)	.10*
Death	2 (5)	1 (2)	.32*

*Fisher's Exact Test.

Of the 38 high-risk patients aged 6 months or older who were eligible for immunization, only four (11%) had been appropriately immunized with influenza vaccine. All four of these immunized patients had underlying pulmonary disease. None of the high-risk patients received amantadine as prophylaxis or treatment. Examining morbidity based on the length of hospitalization, 19 patients (44%) in the high-risk group were hospitalized for 14 days or more compared with six patients (11%) in the low-risk group. This difference was significant at $P<.001$. When the length of hospitalization for patients with nosocomial influenza infections was excluded, this difference still remained significant at $P<.001$ (Table 2).

Nosocomial or hospital-acquired influenza infections were defined as influenza infections in patients who did not have respiratory symptoms at the time of admission but who developed symptoms and had a positive influenza culture 7 or more days after they were admitted to the hospital. Six patients in the high-risk group (14%) had nosocomial influenza infections compared with two patients (4%) in the low-risk group. ($P=.05$ by Fisher's Exact Test; Table 2).

Of the six high-risk patients with nosocomial infections, three had underlying pulmonary disease, two were immunosuppressed, and one had cardiac disease. Of the four high-risk patients who were eligible by age for immunization, none had received the influenza vaccine. There did not appear to be any differences in the rate of nosocomial acquisition between influenza type A and B. The mean length of hospital stay at the time cultures were obtained in these patients was 58 days.

Morbidity in these patients was also assessed in terms of the need for intubation directly related to their influenza infection. Four patients (9%) in the high-risk group compared with only one patient (2%) in the low-risk group required intubation. All four of the high-risk patients who were intubated had underlying pulmonary disease. None of the patients who were eligible by age had been immunized with influenza vaccine. Two home ventilator–dependent patients who required hospitalization in the intensive care unit because of increasing ventilatory settings due to influenza infections were not included in this analysis.

Mortality in the cohort was also assessed. Three patients died, resulting in a mortality rate of 3%. Two of these patients met the criteria for the high-risk group. The first patient was a 3-month-old infant with atrioventricular canal who died after 10 days of an influenza B infection. The second patient was a 12-year-old child with restrictive lung disease, juvenile dermatomyositis, and calcinosis universalis. She became infected with influenza A via nosocomial spread after being in the hospital for 175 days and died 7 days later. She had not been immunized with the influenza vaccine.

In summarizing the morbidity from influenza in high-risk, vaccine-eligible patients (aged 6 months or older), there were more patients with pulmonary disease (66%) than other high-risk conditions. These patients also had a longer mean length of hospital stay (20 days) than the other high-risk patients, including those with immunodeficiency (mean stay, 15 days), cardiac disease (mean stay, 13 days), renal disease (mean stay, 11 days), and hemoglobinopathy and immunosuppression (mean stay, 8 days each). There were three intubations and one death within the pulmonary group and none in the other high-risk groups in this age range.

Significant morbidity occurred in the high-risk patients younger than 6 months. Of three pulmonary patients, one acquired influenza via nosocomial spread and a second patient required intubation. Of the two cardiac patients, one acquired a nosocomial influenza infection and the second patient died secondary to influenza. Of the five high-risk patients younger than 6 months, four (80%) experienced significant morbidity from influenza.

COMMENT

Our data show that high-risk patients experienced more morbidity from influenza infections than low-risk patients when length of hospitalization and nosocomial influenza infections were considered. Since this was a retrospective study, it was difficult to determine what portions of the hospitalizations were due solely to influenza infections and their sequelae. This statistical difference in length of hospitalization persisted even when the length of hospitalization for patients with nosocomial-acquired influenza was excluded.

The nosocomial acquisition of influenza infections in high-risk patients is undoubtedly related to prolonged hospitalization and exposure to other patients and health care workers with respiratory viral infections. This has important ramifications concerning isolation and immunization policies. Although we cannot draw any conclusions concerning isolation techniques from our study, it does point out that nosocomial spread does occur and has serious consequences. Current recommendations include immunization for health care providers who treat high-risk patients. We do not have data to document health care workers' immunization rates at our institution, but this may remain another way in which nosocomial spread can be minimized. The fact that two of the nosocomial infections occurred in infants younger than 6 months for whom immunization is not recommended suggests that immunization of health care personnel may be essential.

Our sample was too small to compare differences between the high-risk and low-risk patients for the number of intubations and deaths. However, the mortality rate of 3% in our study is consistent with the rates of 1% to 4% found in other studies. Interestingly, cultures yielded both influenza A and B that year, with type B more predominant in our cohort. Although it has been suggested in the literature that type A disease results in more serious morbidity than type B,[14] we did not find this to be the case. Type B disease resulted in four of six nosocomial infections, five of five intubations, and two of three deaths. Influenza A is thought to lead to more morbidity because of its association with antigenic shift. Since no major shifts have occurred in the last few years, we did not expect to note a difference in our cohort. Also, Reye's syndrome has been shown to correlate with cases of influenza B infection.[15,16] There were no cases of Reye's syndrome in our cohort.

It is worth noting that cultures from four immunized patients yielded influenza. Although we did not have the influenza subtypes cultured from these four individuals, the circulating subtypes in the community did match those present in the vaccine that year.[17] The four patients constituted too small a sample for statistical significance to be determined. However, their mean hospital stay was only 8 days, which was much shorter than the 20 days for the remainder of the pulmonary patients. None of the four patients acquired nosocomial influenza infections and none required intubation or died. Although the efficacy of the vaccine is thought to be 70% to 80%, it may be that the disease course is modified secondary to receipt of the vaccine.

The majority of the high-risk patients admitted to the hospital had pulmonary disease, although there were several patients in other high-risk groups. These data may have been biased if more pulmonary patients than other high-risk patients were followed up by physicians who admit to our hospital, but we have no reason to suspect this. Also, the criteria for admission of patients with pulmonary conditions might be less stringent than for other patients. However, since many patients with acute problems are admitted through the emergency department, we would not expect the criteria to depend on subspecialist bias. In addition, other studies[8-10] have shown pulmonary patients to constitute a large proportion of the high-risk patients hospitalized.

We were impressed by the fact that of the five high-risk patients younger than 6 months, one required intubation and a second died. At present, these patients are not eligible for the influenza vaccine. Perhaps further research will lead to the development of a vaccine that can be used in younger children. The only other ways to minimize morbidity in these young high-risk patients is by immunization of caretakers, family members, and hospital personnel.

We need to immunize all high-risk patients; in particular, high-risk pulmonary patients. Immunization should be considered in all high-risk hospitalized patients. Since hospitalized patients are a captive audience and the vaccine is an inactivated viral vaccine, it may be appropriate to immunize patients once their acute symptoms have resolved. Immunization of family members and health care workers needs to be encouraged.

More studies are needed to determine which high-risk children need to be immunized, to develop an effective vaccine in younger infants, and to determine the impact of nosocomial spread and isolation techniques in influenza.

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Ian C. Balfour, MBBS; Ami M. Drimmer, PhD; Soraya Nouri, MBBS;
D. Glenn Pennington, MD; Carol L. Hemkens, RN; Linda L. Harvey, RN

• Sixteen patients participated in a Pediatric/Young Adult Cardiac Rehabilitation Program that included exercise training, education about cardiovascular diseases, dietary counseling, and counseling on stress management. Seven patients completed the program, and complete data were available on six. The subjects demonstrated significant changes in their hemodynamics and exercise tolerance after completing the program. Resting blood pressure decreased by 7%, from 119±12 to 111±10 mm Hg; peak oxygen consumption increased by 20%, from 31.9±4.3 mL/kg of body weight per minute to 38.4±6.0 mL/kg of body weight per minute; and exercise treadmill time increased by 21%, from 8.5±1.4 to 10.3±1.0 minutes. No complications occurred during exercise training or testing. Supervised exercise training at moderate intensity is safe and produces significant and beneficial changes in hemodynamics and exercise time in children with cardiac disease.

(*AJDC.* 1991;145:627-630)

Cardiac Rehabilitation Programs (CRPs) are recognized as valuable for the treatment of adults with cardiac disease.[1] Recently, similar programs have been developed for children.[2,3] The CRP at Cardinal Glennon Children's Hospital/St Louis (Mo) University Medical Center was developed for children and young adults with congenital or acquired cardiac disease, children with increased risk of developing coronary disease, and chronically ill children who might benefit from exercise training. The goals of the program are similar to those of the American College of Cardiology[4]: (1) to help individuals attain optimal physiologic and psychologic function; (2) to reverse the adverse physiologic effects of deconditioning that result from an overprotected, sedentary lifestyle; (3) to encourage the patient and family through education to adopt a life-style that may reduce the risk of coronary heart disease and hypertensive cardiovascular disease, including avoiding smoking, controlling blood pressure and diabetes mellitus, and decreasing emotional stress, and to educate the patient and family about cardiovascular disease and the importance of a program of suitable and regular physical activity; (4) to reduce the emotional disorders that often accompany serious and chronic health disorders; and (5) to reduce the cost of health care by diminishing physical and psychological disability and the need for medical treatment.

PATIENTS AND METHODS

The CRP at Cardinal Glennon Children's Hospital/St Louis University Medical Center is a 3-month program that combines exercise training, dietary counseling, counseling on stress management, and education concerning cardiovascular physiology and congenital and acquired cardiovascular diseases. Family members are encouraged to participate in the program, particularly in the educational sessions. Most participants were referred to this facility from the Cardiology Clinic at Cardinal Glennon Children's Hospital, but patients also were referred from other clinics (eg, the Renal Clinic). Before entering the program, patients were encouraged to set reasonable goals: improved fitness, weight loss, etc. Informed consent was obtained from the participants' parents. Each patient was evaluated by a pediatric cardiologist. An electrocardiogram and chest roentgenogram were obtained in each case. When indicated, patients also underwent Holter monitoring and echocardiography as part of their preparticipation evaluations. All patients underwent a graded maximal exercise treadmill test (Bruce protocol)[5] to evaluate their exercise tolerance and cardiovascular fitness. During the exercise test, the patient's time on the treadmill, heart rate, blood pressure, and electrocardiographic results were recorded. Metabolic parameters, oxygen consumption ($\dot{V}o_2$), and carbon dioxide production ($\dot{V}co_2$) also were measured using a metabolic cart (Beckman Instruments Inc, Anaheim Calif). Metabolic measurements were obtained at 15-second intervals during the exercise test. The highest measured $\dot{V}o_2$ after the patient has reached anaerobic threshold is the patient's peak $\dot{V}o_2$. Anaerobic threshold was regarded as the point at which the $\dot{V}co_2$-$\dot{V}o_2$ ratio reached or exceeded 1.0 and a sharp rise in the $\dot{V}co_2$-$\dot{V}o_2$ curve occurred when this ratio was plotted against time. Using the data from the exercise test, an exercise program was prescribed for each patient. The exercise programs were individualized to meet the abilities, needs, and goals of each patient. The program emphasized dynamic exercise (eg, walking and riding a stationary bicycle). Patients were encouraged to exercise strenuously enough to increase and maintain heart rates of 70% or more of their maximal heart rates. Supervised exercise sessions were held 3 days per week, and patients were encouraged to exercise at home on 1 or 2 additional days. The sessions lasted 30 to 40 minutes and were supervised by exercise trainers who were registered nurses, an exercise physiologist, and a physician. The initial and final 10 minutes of each exercise session were used as "warm-up" and "cool-down" periods during which stretching exercises were done. Patients at risk of developing dysrhythmias were screened with telemetry and Holter monitoring during their first three sessions. Patients were taught to monitor their responses to exercise by counting their pulse rates and to monitor exercise intensity using Borg's scale of perceived exertion.[6] Initially, the program was structured to last 6 months, with 56 sessions. Subsequently,

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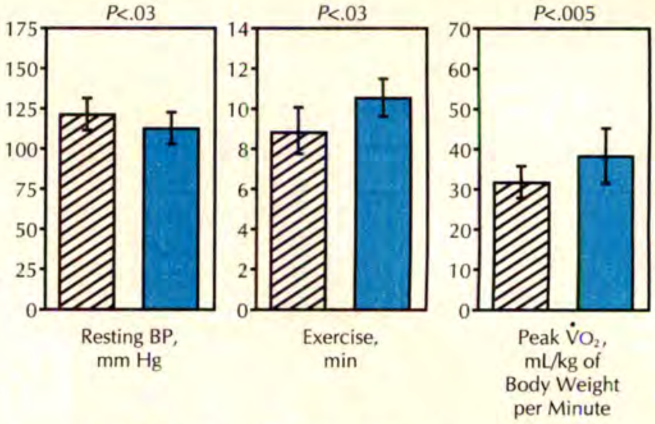
From the Departments of Pediatrics/Adolescent Medicine (Drs Balfour and Nouri and Ms Harvey) and Surgery (Dr Pennington) and the Cardiovascular Fitness and Rehabilitation Center (Dr Drimmer and Ms Hemkens), St Louis (Mo) University Medical Center.

Reprint requests to St Louis University Medical Center, Department of Pediatrics/Adolescent Medicine, 1465 S Grand Blvd, St Louis, MO 63104 (Dr Balfour).

Table 1.—Data of Patients Who Did Not Complete the Cardiac Rehabilitation Program

Patient No.	Diagnosis*	Age, y	Reason for Not Completing Program
1	DC, obesity	16.3	Insufficient interest
2	Mild AS, obesity	12.8	Insufficient interest
3	TOF (repaired)	7.8	Insufficient interest
4	IHSS, obesity	18.6	No transportation
5	Hypertension	14.2	No transportation
6	AVR	10.6	Torsion of testes
7	VSD	14.4	Sprained ankle
8	VSD	7.3	Travel
9	MVP	16.1	Family problems
10	Fontan	9.9	Completed program (follow-up test not suitable for analysis)

*DC indicates dilated cardiomyopathy; AS, aortic stenosis; TOF, tetralogy of Fallot; IHSS, idiopathic hypertrophic subaortic stenosis; AVR, aortic valve replacement; USD, ventricular septal defect; MVP, mitral valve prolapse; and Fontan, Fontan procedure for tricuspid atresia.



Patients' mean resting systolic blood pressure (BP), exercise time, and peak oxygen consumption ($\dot{V}\,o_2$) before (hatched bars) and after (solid bars) rehabilitation exercise tests. Vertical lines intersecting the bars indicate SD.

it was shortened to 3 months and 36 sessions to improve patient compliance. The exercise test and metabolic measurements were repeated at the end of the program. Seven patients completed the CRP, and six underwent satisfactory preparticipation and postparticipation evaluations.

Dietary intervention was an important aspect of the program. On entry, each participant was directed to keep a 3-day food log. This was reviewed by a dietitian, and the patient and family were advised on making dietary changes when necessary to reduce cardiovascular risk factors, control weight gain, or promote weight loss. Parents and patients also were evaluated by a psychologist and instructed in stress management through relaxation and biofeedback techniques.

The preparticipation and postparticipation test data were compared using the Student's paired *t* test.

RESULTS

Sixteen patients were enrolled in the program. Their diagnoses are listed in Tables 1 and 2. All patients were ignorant about appropriate exercise and anxious about exercise. Complete data from preparticipation and postparticipation exercise tests were available on six patients, aged 13.5 to 19.8 years (mean, 17.3±2.8 years), who completed an average of 29 sessions. One patient completed the program, but results of his follow-up exercise test were unsuitable for analysis because it was a submaximal test. Nine patients either did not complete the program or completed the program but did not undergo follow-up tests. These latter patients took part in an average of 18 sessions. There were many reasons for patients not completing the program (Table 1). Of the six patients who completed the program and had satisfactory preparticipation and postparticipation tests, three had undergone successful repair of congenital heart defects, and three had not undergone cardiac surgery (Table 2). The preparticipation and postparticipation evaluations of these patients are shown in Table 2 and the Figure. No significant differences were observed in the subjects' mean resting heart rates, mean peak heart rates, or mean peak blood pressures when their prerehabilitation and postrehabilitation exercise test results were compared. The subjects' resting systolic blood pressures decreased (as measured by a sphygmomanometer) after training. As a group, the patients significantly improved in exercise time and peak $\dot{V}o_2$ (Figure). One patient did not improve in these parameters. This patient had been a very active adolescent boy when he developed sudden-onset severe chest pain and electrocardiographic changes suggestive of an anterior-septal myocardial infarct. He was thought to have had myocarditis. Results of a cardiac muscle biopsy were normal, and he eventually recovered completely. This patient did not have structural cardiac disease and probably did not exercise strenuously enough to improve his conditioning level.

COMMENT

Physical activity (play or recreational sports) is important for the normal development and general well-being of children[7,8] and may help prevent coronary heart disease.[9] Many children with heart disease remain sedentary even after successful repair of congenital defects or recovery from acquired diseases such as myocarditis. Because the activity of these children may have been restricted for many years, they and their families may be apprehensive about their participation in normal physical activity. The psychological adjustment a child makes to a chronic disease is primarily determined by parental anxiety and pampering rather than by the severity of the illness.[7,8] By participating in a rehabilitation program that includes education, the child and the family are shown exercises that are safe, ways of monitoring the severity of exercise, and ways of measuring the body's response to exercise. Thus, the undue anxiety of the family may be alleviated, and the child's illness viewed in a more pragmatic manner. Rehabilitation that includes exercise training may also improve exercise tolerance and cardiovascular function[10,11] and reduce risk factors for coronary heart disease.[9] Matthews et al[2] demonstrated that exercise training by four pediatric cardiac patients increased maximal oxygen consumption and decreased total serum cholesterol levels. The patients' and their mothers' psychologic outlooks in terms of fear of death and apprehension about exercise improved. Bradley et al[3] also have reported increased $\dot{V}o_2$, treadmill time, and peak systolic blood pressure after exercise training by patients who had undergone repair of tetralogy of Fallot and transposition of the great arteries.

Normal subjects exhibit many physiologic changes after training, such as increased exercise time and peak $\dot{V}o_2$, which are due in part to an increase in maximal cardiac output.[11-13] Because maximal heart rate does not change

Table 2.—Data of Patients Who Completed the Cardiac Rehabilitation Program*

			Before Program			After Program		
Patient No.	Diagnosis	Age, y	Resting SBP, mm Hg	Peak $\dot{V}o_2$, mL/kg of Body Weight per Minute	ETT, min	Resting SBP, mm Hg	Peak $\dot{V}o_2$, mL/kg of Body Weight per Minute	ETT, min
11	Fontan	19.8	128	28.7	7.75	125	30.5	9.28
12	Mild AS, obesity	14.3	110	32.6	8.13	100	44.1	10.37
13	PVCs, obesity	13.5	98	31.6	7.13	100	36.0	9.22
14	PS	18.3	120	25.9	7.18	113	32.5	9.80
15	Myocarditis (resolved)	18.2	127	38.5	11.10	108	39.1	11.10
16	AVR	18.9	128	33.8	8.50	120	48.4	11.40

*SBP indicates systolic blood pressure; $\dot{V}o_2$, oxygen consumption; ETT, exercise treadmill time; Fontan, Fontan procedure for tricuspid atresia; AS, aortic stenosis; PVCs, premature ventricular contractions; PS, pulmonary stenosis; and AVR, aortic valve replacement.

with training and cardiac output equals heart rate multiplied by stroke volume, stroke volume must increase to change cardiac output. An increase in myocardial contractility would explain the increased stroke volume, but this has not been proven.[12,13] Patients with congenital heart disease, even those who have undergone repair for the condition, may not be capable of responding as normal subjects would, although they demonstrate similar physiologic changes. For example, a study[14] of patients who underwent the Fontan procedure for tricuspid atresia showed that those patients in whom the right ventricle was incorporated as part of the repair (right atrium to ventricle to pulmonary artery anastomosis) were not able to increase their stroke volumes during exercise as well as those patients who had direct anastomoses from right atrium to pulmonary artery. The participants in our study improved their exercise times and peak $\dot{V}o_2$ and sustained decreases in their resting systolic blood pressures. A decrease in peripheral resistance (afterload), resulting in a decrease in the work of the left ventricle, is another physiologic change observed in normal subjects that may lead to increased stroke volume.[10,11] As a group, our patients demonstrated lower resting systolic blood pressures after training, indicating a reduction in peripheral resistance. This could have been the result of lower catecholamine levels. Studies in adult patients[15,16] have shown that training lowers the levels of these hormones at rest and during exercise. Peripheral resistance may also decrease because of the development of new capillaries in the trained skeletal muscle, which increases the total cross-sectional area of the vascular bed, a phenomenon previously demonstrated in animal studies.[10] Whatever the mechanism, training may produce physiologic changes that increase maximal cardiac output. This allows more oxygen to be taken up from the lungs for delivery to the exercising muscles. Additionally, the skeletal muscles may undergo changes such as an increase in the number of mitochondriae and the level of metabolic enzymes. Such changes improve the aerobic capacity and endurance of the trained muscle by causing more oxygen to be extracted from the blood.[10] With more oxygen available during exercise, exercise time and peak $\dot{V}o_2$ increase.

Hagberg et al[17] and others[18,19] have demonstrated the antihypertensive effect of exercise. Therefore, in addition to a beneficial effect on cardiac performance, exercise training may lower risk factors such as hypertension that contribute to the development of atherosclerotic disease. The resting heart rates of our patients did not decrease. A reduction in resting heart rate is usually observed in normal subjects after training.[11,12] Perhaps the exercise program was not long enough or intense enough to induce changes in heart rate, or these patients, in association with structural heart disease, had sinus node dysfunction.

The program's success in achieving physiologic changes in patients was limited by the relatively large number of patients who did not complete the protocol. Two patients developed coincidental medical illnesses unrelated to their cardiac conditions or to the CRP exercises (one patient developed testicular torsion and another sprained her ankle while at school), so their absences were unavoidable. The remaining patients who did not complete the program cited many preventing factors, including family problems, an out-of-state visit to a noncustodial parent, transportation problems, and lack of interest. We have made some changes in the program to improve compliance. Its duration has been shortened from 6 to 3 months. We encourage parents to participate in the exercise classes whenever possible (after obtaining appropriate medical clearance). The number of educational sessions has been increased to improve parental participation. Future programs will be held in fall only, rather than year-round. This may prevent conflicts with summer vacation plans and the difficulty in transportation during the winter. Another problem is the cost of maintaining the staff and facilities necessary for the program. We limited the cost by sharing the facilities and staff with an Adult Cardiac Rehabilitation Program, and if at any time fewer than five patients were enrolled, the pediatric exercise sessions were combined with those of the adult cardiac patients.

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In Other AMA Journals

JAMA

Clinical and Laboratory Correlates of *Pneumocystis carinii* Pneumonia in Children Infected With HIV

E. Connor; M. Bagarazzi; G. McSherry; B. Holland;
M. Boland; T. Denny; J. Oleske
(*JAMA.* 1991;265:1693)

CD4 T-Lymphocyte Counts and *Pneumocystis carinii* Pneumonia in Pediatric HIV Infection

A. Kovacs; T. Frederick; J. Church;
A. Eller; M. Oxtoby; L. Mascola
(*JAMA.* 1991;265:1698)

Prevalence of HIV Infection in Childbearing Women in the United States

M. Gwinn; M. Pappaioanou; J. R. George; W. H. Hannon;
S. C. Wasser; M. A. Redus; R. Hoff; G. F. Grady;
A. Willoughby; A. C. Novello; L. P. Petersen;
T. J. Dondero, Jr; J. W. Curran
(*JAMA.* 1991;265:1704)

Trends of HIV Seroconversion Among Young Adults in the US Army, 1985 to 1989

J. G. McNeil; J. F. Brundage; L. I. Gradner; Z. F. Wann;
P. O. Renzullo; R. R. Redfield; D. S. Burke;
R. N. Miller; US Army Retrovirus Research Group
(*JAMA.* 1991;265:1709)

Opinion Leaders vs Audit and Feedback to Implement Practice Guidelines: Delivery After Previous Cesarean Section

J. Lomas; M. Enkin; G. M. Anderson;
W. J. Hannah; E. Vayda; J. Singer
(*JAMA.* 1991;265:2202)

Article

Dietary Calcium and Bone Mineral Status of Children and Adolescents

Gary M. Chan, MD

• **We studied 164 healthy, white children aged 2 to 16 years; there were 88 boys and 76 girls. By the method of single photon absorptiometry, we found that age, height, and weight correlated positively with bone mineral content of the radius bone. In the children's diet, most of those aged 2 to 11 years met the recommended dietary allowance (800 mg daily) for calcium. Children older than 11 years had low dietary calcium intake; only 15% met the recommended dietary allowance for calcium (1200 mg daily). Dietary calcium intake was associated with bone mineral status. Children ingesting more than 1000 mg of calcium daily had higher bone mineral content than those ingesting less. Almost all serum determinations of calcium, phosphate, magnesium, alkaline phosphatase, parathyroid hormone, 25-hydroxyvitamin D, and 1,25-dihydroxyvitamin D were within normal limits and had no correlation with children's bone mineral status.**

(*AJDC.* 1991;145:631-634)

Calcium is the most abundant mineral in the human body. Ninety-nine percent of the body's calcium is found in the bones and teeth. It is an essential nutrient for growth during infancy and childhood.[1] Skeletal growth and development may be the most important concern in nutrition for children. From birth to age 20 years, the bones are in a phase of active growth. Peak bone mass is achieved between ages 12 and 40 years.[2]

There are little data on the role of calcium nutrition in bone status in children during this crucial period. Children need to receive sufficient calcium for building bone mass. The purpose of this study was to investigate the nutritional and biochemical factors that may affect children's bone mineral status.

SUBJECTS AND METHODS

Subjects

All children were recruited from the author's private pediatric clinic and local schools. The subjects were healthy, white, and free of any medications that may affect calcium metabolism. None of the children reported smoking or consuming alcohol. Children aged 2 to 16 years were eligible for the study. All children were within the 10th and 90th percentiles for weight and height, respectively, recommended by the National Center for Health Statistics.[3] This study was approved by our institutional review board. Informed consent was obtained from the children's parents and assent of the older children.

Experimental Design

Each child was seen twice during a 3-month period. At each visit, routine weight and height were recorded. A 2-day dietary history (home diet diary) was taken 3 days prior to the office visit. Each child's history was checked by a dietitian and verified by the parents. Food brands and amounts were recorded. All dietary records were coded and checked by our dietitian, who was blinded to the study's results. These records were then evaluated by a dietary computer program (Nutripractor, San Diego, Calif). All dietary and anthropometric values obtained at each visit were averaged and used in the final analyses.

Blood was drawn once during the study by venipuncture for measurements of serum concentrations of calcium, phosphate, magnesium, alkaline phosphatase, parathyroid hormone, 1,25-dihydroxyvitamin D, and 25-hydroxyvitamin D. All blood samples were drawn in the afternoon between 1 and 4 PM after the bone mineral analysis. The methods for analysis of calcium, phosphate, magnesium, alkaline phosphatase, 1,25 dihydroxyvitamin D, and 25-hydroxyvitamin D have been described previously.[4] Our children's normal range for 1,25-dihydroxyvitamin D was from 34 to 220 pmol/L. The parathyroid hormone assay (Nichols Institute Diagnostic, San Pedro, Calif) uses the goat antisera that recognize primarily the C-terminal of the molecule. Our normal parathyroid hormone range was 6 to 32 pmol/L.

Bone mineral status was determined for all subjects by the method of photon absorptiometry using the Lunar bone mineral analyzer (Lunar Corp, Madison, Wis). The analyzer consists of a scanner module containing a narrow collimated scintillation detector and an iodine 125 radionuclide source. As the scanner moves across the bone to be measured, the scintillation detector counts the attenuated counts, and the absorbance of the photons is proportional to the bone mineral content (BMC) in grams per linear centimeter. The bone width is also measured, as it is proportional to the length of the scan path over the bone. The nondominant radius was measured at the midshaft (distal third) site. The bone was measured once during the study. In adults and infants, this method correlates very highly with the ash weight of the bone,[5] and has been correlated with total body calcium ($r = .85$).[6] In our laboratory, the day-to-day error rate in infants and adults is 2.5%.

Statistical Analysis

All statistical analyses were performed with a commercially available computer program (Statworks, Philadelphia, Pa). Standard *t* tests and analysis of variance were used for comparison between groups. The correlations between variables were analyzed with regression analysis. Multivariate analyses were performed when two or more independent variables influenced BMC. To compare bone mineral data at different ages, the children's ages were arbitrarily divided into five age categories, and

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From the Department of Pediatrics, University of Utah Medical Center, Salt Lake City.

Reprint requests to Department of Pediatrics, 2A210, University of Utah Medical Center, Salt Lake City, UT 84132 (Dr Chan).

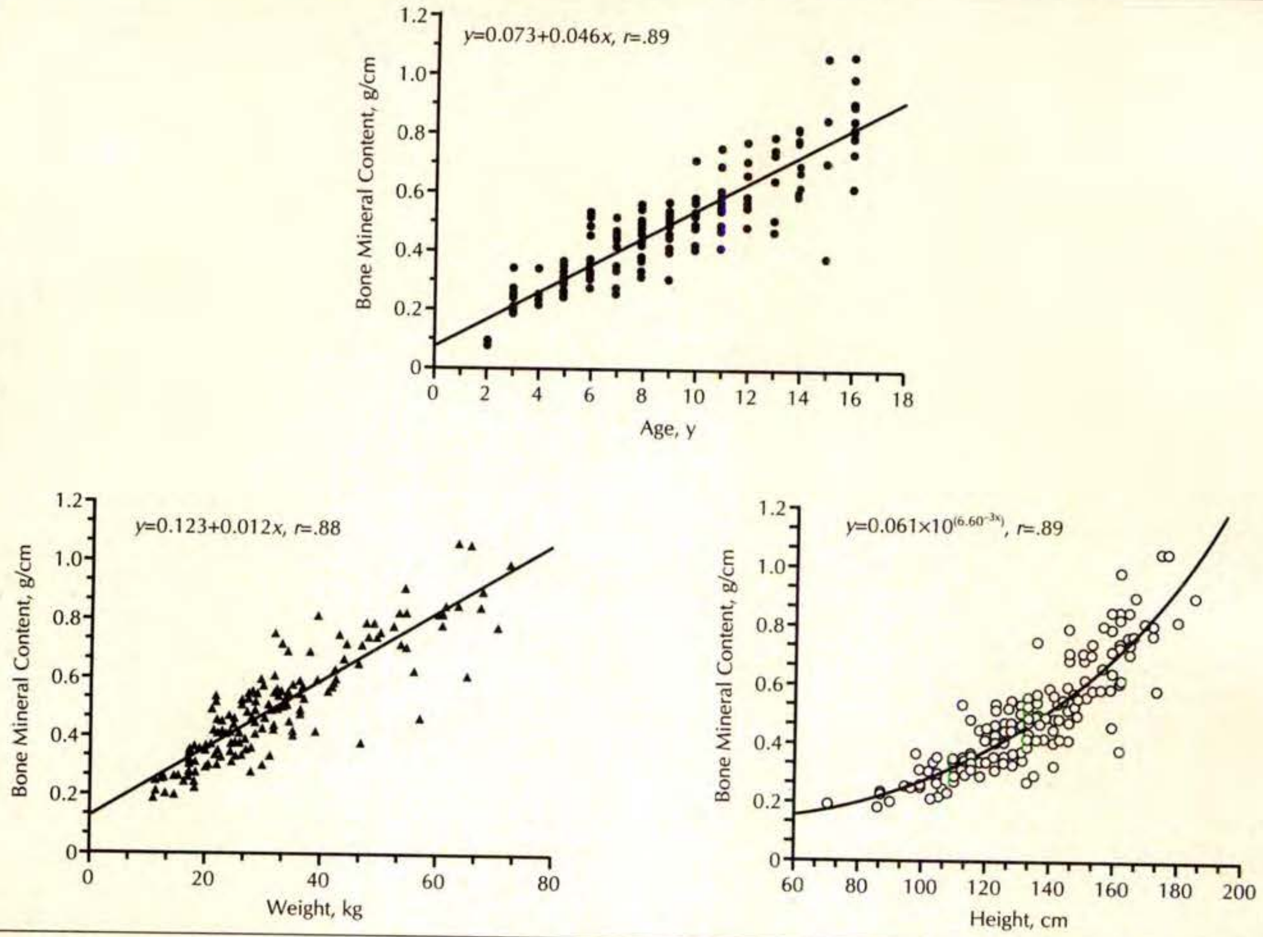

Fig 1.—*Relation of weight, height, and age to bone mineral content in 164 children. Correlation was significant for all three variables.*

Table 1.—Children's Daily Dietary Intakes

	Mean (±SD) Intakes					
Age, y	**Total Energy, kJ**	**Protein, g**	**Calcium, mg**	**Phosphate, mg**	**Sodium, mg**	**Magnesium, mg**
2-5	316.9±0.23	56±21	1126±566	1181±510	2006±786	255±265
6-8	350±75	61±16	1075±368	1206±389	2176±930	213±165
9-11	364.3±0.23	65±21	966±361	1154±371	2294±856	180±63
12-14	445.7±140.7	72±18	1179±485	1307±418	2165±801	208±61
15-16	394.0±168.8	64±28	925±524	1121±496	2054±936	178±80

a *z* score or standard normal variate was determined for each BMC value within each age category. The *z* score is a measure of the deviation from the expected population mean.

RESULTS

Description of Subjects

Eighty-eight boys and 76 girls aged 2 to 16 years completed the study. No drugs, tobacco, or alcohol were reported to be taken by our subjects. The mean age (±SD) of our children was 9.1±3.6 years.

Relation of Age, Weight, Height, and Sex to Bone Mineral Status

Age, weight, and height correlated with bone mineral status ($r=.88$ to .89; $P<.01$; Fig 1). The exponential equation improved the fit of the height data over the linear equation from $r=.86$ to $r=.89$. Boys had a higher BMC status than girls, their mean *z* score being 0.106 and the girls' mean *z* score being −0.123 ($P<.001$). After controlling for weight, there were no differences between bone mineral status of boys vs girls as determined by their *z* scores.

Relation of Diet to Bone Mineral Status

Children's dietary intakes are shown in Table 1. There was no difference between the two diet histories, and no association between dietary intakes and ages of the subjects. A majority of children (70%) younger than 11 years were consuming at least the recommended dietary allowance for calcium, 800 mg daily. However, 63% of children older than 11 years were not consuming the recommended dietary allowance for calcium, 1200 mg daily. Girls older than 11 years had a mean daily dietary calcium intake of 750±450 mg; only 15% of the girls and 53% of the boys met the recommended dietary allowance for calcium. The differences in calcium intake between girls and boys older

Table 2.—Children's Mean Serum Values and Ranges*

Age, y	Total Calcium, mmol/L	Phosphate, mmol/L	Magnesium, mmol/L	Alkaline Phosphate, IU/L	25-OH D, mmol/L	1,25 $(OH)_2D$, pmol/L	PTH, pmol/L
2-5	2.4(2.2-2.7)	1.6(1.2-2.0)	1.1(0.9-1.4)	123(60-220)	82(55-110)	136(61-238)	6(3-9)
6-8	2.3(1.7-2.8)	1.7(0.8-3.6)	1.2(0.9-1.4)	91(33-277)	65(40-102)	117(34-243)	9(3-18)
9-11	2.3(1.6-2.8)	1.7(0.7-2.6)	1.1(0.8-1.2)	100(33-222)	68(32-112)	112(46-294)	7(2-18)
12-14	2.3(1.6-2.7)	1.5(0.9-2.6)	1.1(0.8-1.2)	12(50-191)	62(8-110)	122(44-199)	9(2-18)
15-16	2.3(1.6-2.7)	1.3(0.5-1.8)	1.1(0.8-1.5)	63(21-155)	72(35-138)	122(68-275)	9(2-22)
Normal range	2.2-2.7	1.1-1.7	0.6-1.2	47-112	25-150	34-792	6-32

*25-OH D indicates 25-hydroxyvitamin D; 1,25 $(OH)_2D$, 1,25-dihydroxyvitamin D; and PTH, parathyroid hormone. Values in parentheses represent ranges.

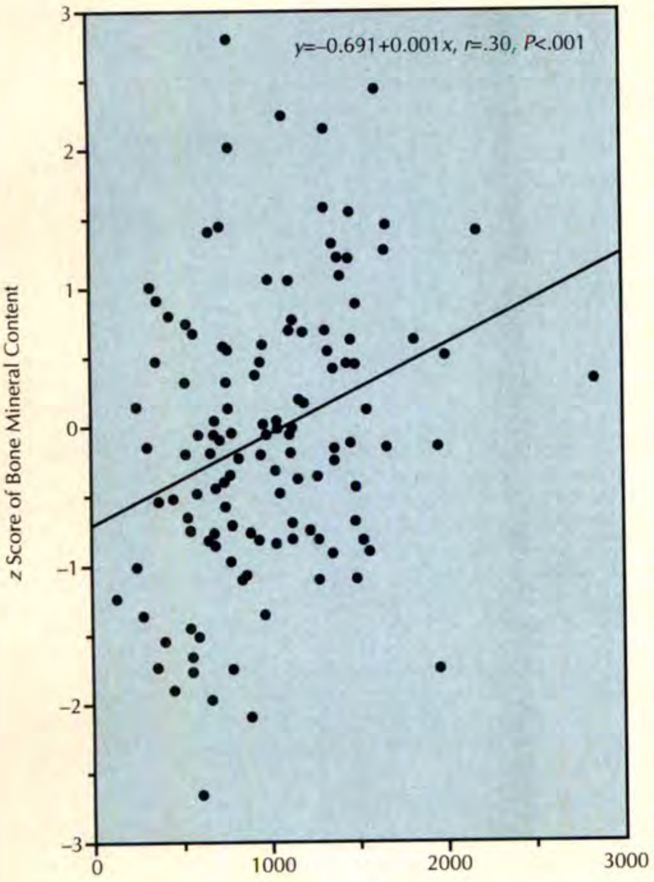

Fig 2.—*z Score of bone mineral content and daily calcium intakes in children. A z score of zero or the average bone mineral content corresponded to a dietary calcium intake of 1000 mg daily.*

than 11 years was not significant ($P<.13$). In children older than 11 years, the z score of the girls' BMCs was not lower than that of boys' BMCs. Of all the nutrients analyzed, only dietary calcium, phosphate, and protein intakes were associated with the z scores of the bone mineral data. All three variables were highly associated with each other. The multiple correlation coefficient of the z score on dietary calcium, phosphate, and protein intakes was .277 ($P=.02$). However, by multivariate analyses, only dietary calcium intake was related to the children's bone mineral status (partial correlation coefficient, .18, $P<.05$) after adjusting for phosphate and protein intakes. By regression analysis, a dietary calcium intake of 1000 mg corresponded to a z score of zero or the average BMC (Fig 2).

Children consuming at least 1000 mg of calcium daily had a higher BMC than those consuming less. The z score of children ingesting less than 1000 mg of calcium daily was -0.30 ± 1.03 compared with 0.21 ± 0.91 for children ingesting more than 1000 mg of calcium daily ($P=.001$ by t test). The difference between these two groups represents 0.51 z units or 0.51 SDs from the mean BMC of each group.

Relationship of Biochemical Values to Bone Mineral Status

Serum values of calcium, phosphate, magnesium, alkaline phosphatase, and vitamin D did not correlate with bone mineral status. Almost all (>90%) serum values were within the normal range (Table 2).

COMMENT

In this study, we have demonstrated that children's bone mineral status was associated with age, weight, height, and dietary calcium intake. Other investigators have shown that BMC is associated with age, weight, and height in children aged 4 to 16 years.[7]

Other factors reported to affect skeletal mass are race and genetics. Some studies have shown that young black children have higher skeletal mass than white children by roentgenographic films and other morphological indexes.[8,9] Because all our subjects were white, we could not evaluate the effect of race on children's bone status. Other ethnic populations may differ from our population. Adult studies on osteoporosis have shown a familial resemblance in bone mass.[10,11]

In our study of children aged 2 to 16 years, BMC increases exponentially with age, weight, and height. Bone mass should normally increase as the child grows. From birth to age 20 years, the skeleton is in an active phase of growth. Peak bone mass is determined in these early years.[2] There were no differences in bone mineral status between boys and girls in our study after controlling for weight. Other researchers in Wisconsin and Ohio have reported a lower bone mineral status in girls.[12,13] In adults, the influence of sex hormones may play a bigger part in the difference of bone mass between men and women.[14]

Dietary intakes of calcium, phosphate, vitamin D, protein, and copper are important nutrients in bone mineralization.[1,2,15] In the present study, only dietary calcium intake appears to contribute to bone mineral status in children. The limited sample size may have affected the detection of other nutrients in children's diet contributing to bone mineralization. Dietary histories generally produce higher estimates of group mean intakes than weighed food records.[16] However, calcium, phosphorus, and protein determinations from dietary histories have shown minor daily variations compared with food records.[17] In the present study, children ingesting more than 1000 mg of calcium daily had higher BMC than those ingesting less. The dietary calcium intake of our children younger than 11 years old was better than that of those who were older. Children, especially adolescent girls older than 11 years, had low calcium intakes. This low calcium intake in school-age children has been reported by others.[18,19] Dairy consumption, which is our major source of calcium, has continued to decline in the United States with the substitution of soft drinks. Some studies in children and adults have shown a relation between dietary intakes of milk and calcium and bone mineral status.[20-22] Increased milk consumption in childhood and adolescence may prevent low postmenopausal bone density.[23]

In children, it may be important to achieve optimal bone mass. There is preliminary evidence to suggest that sufficient intake of calcium and phosphate increases the mineral content in children's bones and might decrease the risk of accidental fractures.[24] Supplemental dietary calcium has also been shown to prevent bone loss during lactation in adolescents.[4] Low peak bone mass rather than excessive loss of bone also may be the major contributor to osteoporosis. Our study has shown that the majority of older children's diets are low in calcium intake, and this low calcium intake may affect their bone mineral status.

This study was supported in part by the National Dairy Council, Rosemont, Ill.

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In Other AMA Journals

ARCHIVES OF OTOLARYNGOLOGY—HEAD & NECK SURGERY

The Canadian Health Care System

Patrick J. Doyle, MD
(*Arch Otolaryngol Head Neck Surg.* 1991;117:495)

Who Ought to Get Decent Health Care?

Ronald A. Carson, PhD
(*Arch Otolaryngol Head Neck Surg.* 1991;117:496-497)

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See brief summary of prescribing information on adjacent page.

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Cough Syrup

IN BRIEF:

Indications and Usage: For relief of coughs and upper respiratory symptoms, including nasal congestion, associated with allergy or the common cold.

Contraindications: Hypersensitivity to any of the ingredients. Do not use in the newborn, in premature infants, in nursing mothers, in patients with severe hypertension or severe coronary artery disease, or in those receiving monoamine oxidase (MAO) inhibitors.

Antihistamines should not be used to treat lower respiratory tract conditions including asthma.

Warnings: Especially in infants and small children, antihistamines in overdosage may cause hallucinations, convulsions, and death.

Antihistamines may diminish mental alertness. In the young child, they may produce excitation.

Precautions: ***General:*** Because of its antihistamine component, Dimetane DX Cough Syrup should be used with caution in patients with a history of bronchial asthma, narrow angle glaucoma, gastrointestinal obstruction, or urinary bladder neck obstruction. Because of its sympathomimetic component, Dimetane DX Cough Syrup should be used with caution in patients with diabetes, hypertension, heart disease, or thyroid disease.

Information for Patients: Patients should be warned about engaging in activities requiring mental alertness, such as driving a car or operating dangerous machinery.

Drug Interactions: Antihistamines have additive effects with alcohol and other CNS depressants (hypnotics, sedatives, tranquilizers, antianxiety agents, etc.). MAO inhibitors prolong and intensify the anticholinergic (drying) effects of antihistamines. MAO inhibitors may enhance the effect of pseudoephedrine. Sympathomimetics may reduce the effects of antihypertensive drugs.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Animal studies of Dimetane DX Cough Syrup to assess the carcinogenic and mutagenic potential or the effect on fertility have not been performed.

Pregnancy

Teratogenic Effects-Pregnancy Category C

Animal reproduction studies have not been conducted with Dimetane DX Cough Syrup. It is also not known whether Dimetane DX Cough Syrup can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Dimetane DX Cough Syrup should be given to a pregnant woman only if clearly needed.

Reproduction studies of brompheniramine maleate (a component of Dimetane DX Cough Syrup) in rats and mice at doses up to 16 times the maximum human dose have revealed no evidence of impaired fertility or harm to the fetus.

Nursing Mothers: Because of the higher risk of intolerance of antihistamines in small infants generally, and in newborns and prematures in particular, Dimetane DX Cough Syrup is contraindicated in nursing mothers.

Adverse Reactions: The most frequent adverse reactions to Dimetane DX Cough Syrup are: sedation; dryness of mouth, nose and throat; thickening of bronchial secretions; dizziness. Other adverse reactions may include:

Dermatologic: Urticaria, drug rash, photosensitivity, pruritus.

Cardiovascular System: Hypotension, hypertension, cardiac arrhythmias, palpitation.

CNS: Disturbed coordination, tremor, irritability, insomnia, visual disturbances, weakness, nervousness, convulsions, headache, euphoria, and dysphoria.

G.U. System: Urinary frequency, difficult urination.

G.I. System: Epigastric discomfort, anorexia, nausea, vomiting, diarrhea, constipation.

Respiratory System: Tightness of chest and wheezing, shortness of breath.

Hematologic System: Hemolytic anemia, thrombocytopenia, agranulocytosis.

Overdosage: ***Signs and Symptoms:*** Central nervous system effects from overdosage of brompheniramine may vary from depression to stimulation, especially in children. Anticholinergic effects may be noted. Toxic doses of pseudoephedrine may result in CNS stimulation, tachycardia, hypertension, and cardiac arrhythmias; signs of CNS depression may occasionally be seen. Dextromethorphan in toxic doses will cause drowsiness, ataxia, nystagmus, opisthotonos, and convulsive seizures.

Toxic Doses: Data suggest that individuals may respond in an unexpected manner to apparently small amounts of a particular drug. A 2 1/2-year-old child survived the ingestion of 21 mg/kg of dextromethorphan exhibiting only ataxia, drowsiness, and fever, but seizures have been reported in 2 children following the ingestion of 13-17 mg/kg. Another 2 1/2-year-old child survived a dose of 300-900 mg of brompheniramine. The toxic dose of pseudoephedrine should be less than that of ephedrine, which is estimated to be 50 mg/kg.

Treatment: Induce emesis if patient is alert and is seen prior to 6 hours following ingestion. Precautions against aspiration must be taken, especially in infants and small children. Gastric lavage may be carried out, although in some instances tracheostomy may be necessary prior to lavage. Naloxone hydrochloride 0.005 mg/kg intravenously may be of value in reversing the CNS depression that may occur from an overdose of dextromethorphan. CNS stimulants may counter CNS depression. Should CNS hyperactivity or convulsive seizures occur, intravenous short-acting barbiturates may be indicated. Hypertensive responses and/or tachycardia should be treated appropriately. Oxygen, intravenous fluids, and other supportive measures should be employed as indicated.

Dosage and Administration: Adults and children 12 years of age and over: 2 teaspoonfuls every 4 hours. Children 6 to under 12 years: 1 teaspoonful every 4 hours. Children 2 to under 6 years: 1/2 teaspoonful every 4 hours. Children 6 months to under 2 years: Dosage to be established by physician.

Do not exceed 6 doses during a 24-hour period. Rev. May 1987.

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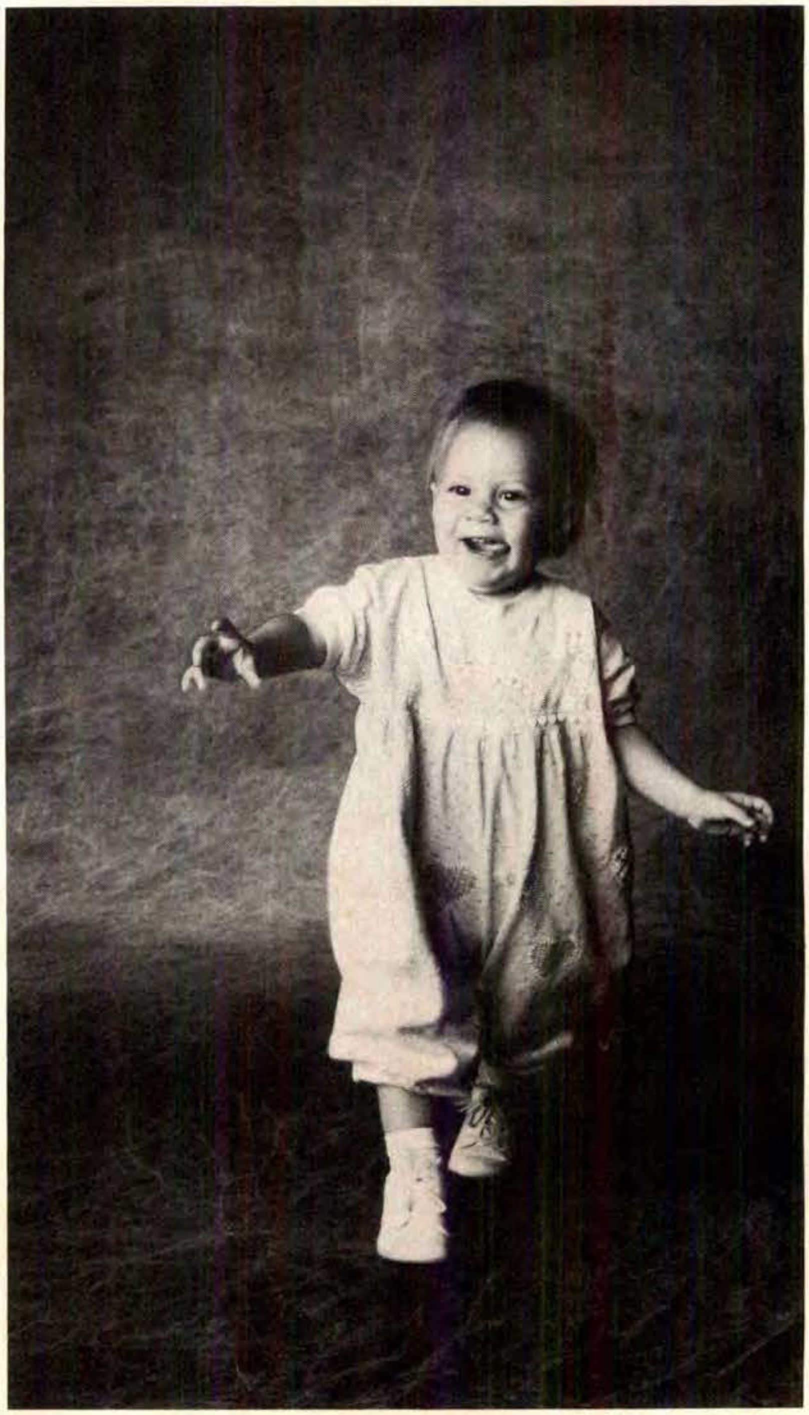

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A booster dose should be administered in infants completing the primary 2-dose regimen before 12 months of age.

PedvaxHIB is contraindicated in patients who are hypersensitive to any component of the vaccine or the diluent.

For a Brief Summary of Prescribing Information, please see next page.

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INDICATIONS AND USAGE: PedvaxHIB is indicated for routine immunization against invasive disease caused by *Haemophilus influenzae* type b in infants and children 2 to 71 months of age.

PedvaxHIB will not protect against disease caused by *Haemophilus influenzae* other than type b or against other microorganisms that cause invasive disease, such as meningitis or sepsis.

Revaccination: Infants completing the primary two-dose regimen before 12 months of age should receive a booster dose (see DOSAGE AND ADMINISTRATION).

Use with Other Vaccines: Studies have been conducted in which PedvaxHIB has been administered concomitantly with the primary vaccination series of DTP and OPV, or concomitantly with M-M-R® II (Measles, Mumps, and Rubella Virus Vaccine Live, MSD) (using separate sites and syringes), or with a booster dose of OPV plus DTP (using separate sites and syringes for PedvaxHIB and DTP). No impairment of immune response to individual tested vaccine antigens was demonstrated. The type, frequency, and severity of adverse experiences observed in these studies with PedvaxHIB were similar to those seen when the other vaccines were given alone.

PedvaxHIB IS NOT RECOMMENDED FOR USE IN INFANTS YOUNGER THAN 2 MONTHS OF AGE.

CONTRAINDICATIONS: Hypersensitivity to any component of the vaccine or the diluent.

WARNINGS: USE ONLY THE ALUMINUM HYDROXIDE DILUENT SUPPLIED. If PedvaxHIB is used in persons with malignancies or in those who are receiving immunosuppressive therapy or who are otherwise immunocompromised, the expected immune response may not be obtained.

PRECAUTIONS: ***General:*** As for any vaccine, adequate treatment provisions, including epinephrine, should be available for immediate use should an anaphylactoid reaction occur. As with other vaccines, PedvaxHIB may not induce protective antibody levels immediately following vaccination. As with any vaccine, vaccination with PedvaxHIB may not result in a protective antibody response in all individuals given the vaccine. As reported with Haemophilus b polysaccharide vaccine and another Haemophilus b conjugate vaccine, cases of Haemophilus b disease may occur in the week after vaccination, prior to the onset of the protective effects of the vaccines. There is insufficient evidence that PedvaxHIB given immediately after exposure to natural *Haemophilus influenzae* type b will prevent illness. Any acute infection or febrile illness is reason for delaying use of PedvaxHIB except when, in the opinion of the physician, withholding the vaccine entails a greater risk.

Laboratory Test Interactions: Sensitive tests (e.g., Latex Agglutination Kits) may detect PRP derived from the vaccine in urine of some vaccinees for up to seven days following vaccination with PedvaxHIB; in clinical studies with PedvaxHIB, such children demonstrated normal immune response to the vaccine.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: PedvaxHIB has not been evaluated for its carcinogenic or mutagenic potential or for its potential to impair fertility.

Pregnancy: *Pregnancy Category C:* Animal reproduction studies have not been conducted with PedvaxHIB. It is also not known whether PedvaxHIB can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. PedvaxHIB is not recommended for use in pregnant women.

ADVERSE REACTIONS: In early clinical studies involving the administration of 8,086 doses of PedvaxHIB alone to 5,027 healthy infants and children 2 months to 71 months of age, PedvaxHIB was generally well tolerated. No serious adverse reactions were reported. During a two-day period following vaccination with PedvaxHIB in a subset of these infants and children, the most frequently reported adverse reactions, excluding those shown in the first table, in decreasing order of frequency, included: irritability, sleepiness, respiratory infection/symptoms, and ear infection/otitis media. Urticaria was reported in two children. Thrombocytopenia was seen in one child. A cause-and-effect relationship between these side effects and the vaccination has not been established.

Selected objective observations reported by parents over a 48-hour period in infants and children 2 to 71 months of age following primary vaccination with PedvaxHIB alone are summarized in the first table.

In The Protective Efficacy Study, 4,459 healthy Navajo infants 6 to 12 weeks of age received PedvaxHIB or placebo. Most of these infants received DTP/OPV concomitantly. No differences were seen in the type and frequency of serious health problems expected in this Navajo population or in serious adverse experiences reported among those who received PedvaxHIB and those who received placebo, and none was reported to be related to PedvaxHIB. Only one serious reaction (tracheitis) was reported as possibly related to PedvaxHIB and only one (diarrhea) as possibly related to placebo. Seizures occurred infrequently in both groups (9 occurred in vaccine recipients, 8 of whom also received DTP; 8 occurred in placebo recipients, 7 of whom also received DTP) and were not reported to be related to PedvaxHIB. The frequencies of fever and local reactions occurring in a subset of these infants during a 48-hour period following each dose were similar to those seen in early clinical studies (see first table).

As with any vaccine, there is the possibility that broad use of PedvaxHIB could reveal adverse reactions not observed in clinical trials.

Potential Adverse Reactions: The use of Haemophilus b polysaccharide vaccines and another Haemophilus b conjugate vaccine has been associated with the following additional adverse effects: early onset of Haemophilus b disease and Guillain-Barré syndrome. A cause-and-effect relationship between these side effects and the vaccination was not established.

Fever or Local Reactions in Subjects 2 to 71 Months of Age Vaccinated with PedvaxHIB Alone: Other Clinical Studies

		Dose 1				Dose 2			
Age (Months)	Reaction	Number of Subjects Evaluated	6 hr.	24	48	Number of Subjects Evaluated	6 hr.	24	48
2-14[*]	Fever >38.3°C (101°F) Rectal	532	2.4%	3.8%	1.9%	329	3.0%	4.3%	3.6%
	Erythema >2.5 cm diameter	1,026	0.2%	1.0%	0.4%	585	0.9%	1.2%	0.7%
	Swelling/ Induration >2.5 cm diameter	1,026	0.6%	1.5%	1.6%	585	0.9%	2.8%	3.7%
15-71[**]	Fever >38.3°C (101°F) Rectal	149	4.0%	4.0%	6.7%				
	Erythema >2.5 cm diameter	572	0.0%	0.3%	0.2%				
	Swelling/ Induration >2.5 cm diameter	572	0.9%	2.1%	1.4%				

[*] Additional complaints reported following vaccination with the first and second dose of PedvaxHIB, respectively, in the indicated number of subjects were: nausea, vomiting, and/or diarrhea (101, 41), crying for more than one-half hour (43, 15), rash (16, 17), and unusual high-pitched crying (4, 4).

[**] Additional complaints reported following vaccination with one dose of PedvaxHIB in the indicated number of subjects were: nausea, vomiting, and/or diarrhea (44), crying for more than one-half hour (19), rash (12), and unusual high-pitched crying (0).

DOSAGE AND ADMINISTRATION:

FOR INTRAMUSCULAR ADMINISTRATION. DO NOT INJECT INTRAVENOUSLY.

2 to 14 Months of Age: Infants 2 to 14 months of age should receive a 0.5-mL dose of vaccine ideally beginning at 2 months of age followed by a 0.5-mL dose 2 months later (or as soon as possible thereafter). When the primary two-dose regimen is completed before 12 months of age, a booster dose is required (see text and second table).

15 Months of Age and Older: Children 15 months of age and older previously unvaccinated against Haemophilus b disease should receive a single 0.5-mL dose of vaccine.

Booster Dose: In infants completing the primary two-dose regimen before 12 months of age, a booster dose (0.5 mL) should be administered at 12 months of age but not earlier than 2 months after the second dose.

DATA ARE NOT AVAILABLE REGARDING THE INTERCHANGEABILITY OF OTHER HAEMOPHILUS b CONJUGATE VACCINES AND PedvaxHIB® (Haemophilus b Conjugate Vaccine [Meningococcal Protein Conjugate], MSD).

Vaccination Regimens by Age Group
(see text for details)

Age (Months) at First Dose	Primary	Age (Months) at Booster Dose
2-10	2 doses, 2 months apart	12
11-14	2 doses, 2 months apart	—
15-71	1 dose	—

TO RECONSTITUTE, USE ONLY THE ALUMINUM HYDROXIDE DILUENT SUPPLIED.

First, agitate the diluent vial; then, using sterile technique, withdraw the entire volume of aluminum hydroxide diluent into the syringe to be used for reconstitution. Inject all the aluminum hydroxide diluent in the syringe into the vial of lyophilized vaccine, and agitate to mix thoroughly.

Withdraw the entire contents into the syringe and inject the total volume of reconstituted vaccine (0.5 mL) intramuscularly, preferably into the anterolateral thigh or the outer aspect of the upper arm.

It is recommended that the vaccine be used as soon as possible after reconstitution. Store reconstituted vaccine in the vaccine vial at 2° to 8°C (36° to 46°F) and discard if not used within 24 hours. Agitate prior to injection.

Parenteral drug products should be inspected visually for extraneous particulate matter and discoloration prior to administration whenever solution and container permit. Aluminum hydroxide diluent and PedvaxHIB when reconstituted are slightly opaque white suspensions.

Special care should be taken to ensure that the injection does not enter a blood vessel.

It is important to use a separate sterile syringe and needle for each patient to prevent transmission of hepatitis B or other infectious agents from one person to another.

HOW SUPPLIED: No. 4792–PedvaxHIB is supplied as a single-dose vial of lyophilized vaccine, NDC 0006-4792-00, and a vial of aluminum hydroxide diluent.

No. 4797–PedvaxHIB is supplied as follows: a box of 5 single-dose vials of lyophilized vaccine, NDC 0006-4797-00, and 5 vials of aluminum hydroxide diluent.

Storage: Before reconstitution, store PedvaxHIB at 2° to 8°C (36° to 46°F). Store reconstituted vaccine in the vaccine vial at 2° to 8°C (36° to 46°F) and discard if not used within 24 hours.

DO NOT FREEZE the aluminum hydroxide diluent or the reconstituted vaccine.

For more detailed information, consult your MSD Representative or see Prescribing Information.
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JOVA08(802)

Chief Resident Training

Developing Leadership Skills for Future Medical Leaders

Robert A. Doughty, MD, PhD; Patricia D. Williams, MD; Charles N. Seashore, PhD

• Most future medical leaders receive little or no formal exposure to management and leadership training activities. Industry invests considerable resources in such training for middle and senior level managers. With the increasing complexity of health care delivery systems and the increased involvement of diverse teams of individuals in the care of patients, it was believed that a training activity designed to enhance participant human interaction skills and teach about group behavior and team management might be valuable to pediatric chief residents. This article describes a 3-day workshop designed to develop such leadership skills. It has been conducted for 3 years with 117 participants. Results of end-of-course and 6-month follow-up evaluations show that participants enjoyed the training experience and believed it was valuable in helping them fulfill their leadership role as chief resident.

***(AJDC*. 1991;145:639-642)**

In recent years, medical educators have increasingly discussed the importance of incorporating human relations skills into medical school curricula and residency training programs.[1-6] At least three issues have contributed to this trend. First, the effects of stress on the emotional well-being of medical students and residents are now recognized as having a potential adverse effect on learning and patient care and, furthermore, may contribute to later physician impairment.[3,4,7] Second, health care consumers are demanding that physicians have effective interpersonal skills.[8-11] Finally, although the traditional model of health care has been a pyramid with the physician as decision-maker issuing orders from the top to those below, health care increasingly involves teamwork among a variety of individuals with differing skills and perspectives.[2,11,12]

Thus, facility in negotiating relationships with many diverse individuals in various group settings promotes optimal learning during medical training and good patient care. Traditionally, however, medical schools and residency programs have done little to address this area of expertise.[13]

The field of organization development grew out of theory and research on the application of behavioral science to work groups and other organizations. In many organizations outside of health care, workshops led by trained facilitators are used to teach executives and managers the principles and practice of effective leadership and teamwork.[14] The successful adaptation of this concept to the "work group" of first-year pediatric residents at a residency program has been described elsewhere.[15]

In this article we describe a leadership training program designed to teach pediatric chief residents skills involving human interaction and the management of teams. Chief residents were targeted for several reasons: first, their role typically requires management skills in which they have little or no experience[13]; second, they serve as teachers and role models for other residents and medical students[2,3,11]; and third, many chief residents subsequently hold important leadership positions in medical education—as attending physicians, program directors, and department chiefs and in such roles, they could foster further training in these areas of leadership skills.

DESCRIPTION

The Pediatric Chief Resident Training Program is a structured, 3-day experiential workshop conducted at sites on the East and West coasts. Content and process are based on organization development techniques and human interaction training methods.[16]

Department Editors.—*Hugh D. Allen, MD, Columbus, Ohio; Fredric Burg, MD, Philadelphia, Pa; Harold Levine, MPA, Galveston, Tex; Barbara Starfield, MD, Baltimore, Md; Larrie W. Greenberg, MD, Washington, DC*

Purpose.—*This department is intended to share information concerning educational efforts in the broad field of pediatrics. We welcome studies on the following topics: undergraduate and graduate education in medicine and allied health occupations; continuing education of health professionals; education of patients and families; and health education for the general public, the community, and organizations that contribute to the promotion and improvement of the health of children.*

Editorial Comment.—*We select our brightest and best to be chief residents, but this new role may require more than handing them a beeper. This article describes a training program designed to teach them how to handle the problems that they may encounter in a management and leadership role.*—H.D.A.

Accepted for publication October 1, 1990.

From the Alfred I. duPont Institute, Wilmington, Del, and Jefferson Medical College, Philadelphia, Pa (Drs Doughty and Williams). Dr Seashore is a private consultant.

Reprint requests to Alfred I. duPont Institute, PO Box 269, Wilmington, DE 19899 (Dr Doughty).

Table 1.—Typical Agenda for Pediatric Chief Resident Training Program

	Time	Activity
Day 1		
	8:30-10:30 AM	Introduction and review of agenda; the role of chief resident
	10:30-12:30 PM	Leadership roles and group functioning
	12:30-1:30 PM	Lunch
	1:30-5 PM	Group process exercise: residency program design
	5-5:30 PM	Midcourse evaluation
Day 2		
	8-10 AM	Personal leadership skills and styles
	10-12:30 PM	Dealing with conflict
	12-1:30 PM	Lunch
	1:30-3 PM	Dealing with conflict (continued)
	3-5:30 PM	Effective feedback
	5:30-7 PM	Dinner
	7-8:30 PM	Stress management; managing the boundary between work and home life
Day 3		
	8-12 PM	Working with hospital administration
	12-1 PM	Lunch
	1-3:30 PM	Hollow square simulation
	3:30-4:30 PM	Review of workshop learnings and applications; reentry to work environment; closure
	4:30-5:30 PM	Written evaluation

The program is offered in the spring to any newly appointed pediatric chief resident who has recently assumed or, in most cases, is about to assume the responsibilities of the position. To date, the program has had 117 participants representing 50 different institutions.

The object of the workshop is to train medicine's future leaders in leadership skills involving human interaction and the management of teams. The basic workshop schedule is given in Table 1. Each workshop's design is modified based on written and verbal feedback obtained during and after the program.

Although the content of each workshop varies depending on group interests and concerns and feedback from previous workshops, a typical session begins with an initial exercise in which participants share ideas and concerns about their new role; this promotes the feeling of the workshop as a "safe" place in which experiences and concerns can be revealed and discussed. Participants thus learn early that sharing in the group fosters mutual learning and support because of the commonality of their experiences and the unique perspectives of each individual.

After the opening exercise, operating norms are suggested and agreed to by all participants. In particular, confidentiality is established as a norm, allowing for open participation and discussion of sensitive topics (eg, personal feelings of incompetence or perceived negative aspects of a particular residency program). Basic theories of group development and experiential learning are introduced with suggestions on how to maximize the educational benefits of the workshop. Next, a session on the dynamics of group function initiates an exploration of general forces that operate in the development and functioning of working groups and applications of this learning to various work groups encountered in the residency setting. The large group is divided into smaller groups that each design a program addressing an area of residency training that participants have identified as problematic, such as resident orientation or resident evaluation systems. Observers note the interpersonal dynamics involved as the groups work to complete their tasks. The exercise affords an opportunity to learn more about the roles individuals take in groups and how those roles can contribute to or detract from effective teamwork as well as provide concrete ideas for implementing changes in each individual's residency program.

The first day concludes with a midcourse evaluation. This session serves two purposes. First, it provides the facilitators with valuable information on whether they need to modify the agenda. Second, it models a technique for giving and receiving feedback that is developed in more depth the next day.

The second morning begins with distribution of individual results on the Myers-Briggs Type Indicator, a self-administered personality instrument that measures an individual's preferences for various styles of perception and decision-making.[17] This is followed by exercises designed to enhance understanding of different style preferences and their effect on professional life.

The theme of appreciating and learning from differences is developed further through administration of the Thomas-Kilmann Conflict Mode Instrument,[18] a self-administered and scored instrument that indicates an individual's preferred styles of managing conflict. Discussion of results is typically followed by a role-playing exercise. The large group is divided into three smaller groups. Each group reconstructs the scenario of a typical conflict situation between a resident and another individual, such as an attending, nurse, parent, or patient. After the three groups reconvene, one group describes its scenario. Residents from the other groups volunteer to act out the scenario. In the ensuing role plays, participants practice a variety of responses to difficult interactions and learn about the advantages and disadvantages of their usual styles.

The afternoon of the second day typically focuses on how to give and receive feedback regarding work performance. Although residents are eager to receive this information from colleagues and supervisors, they are generally unfamiliar with the behaviors required to obtain and give feedback that is nonjudgmental, effective in contributing to improvement in professional skills, and relationship enhancing.

After dinner, the evening is usually devoted to discussion, often in small interest groups, of the stresses of residency training. Typical areas of interest have included the boundary between work and home life, and the different stressors experienced by various groups, such as married and unmarried residents and men and women. The intimacy of the smaller groups followed by sharing in the larger group combine to make this segment uniquely rich in increasing understanding and support for each other.

The morning of the third day is spent on how to work effectively with hospital administration. Small groups again devise role plays addressing significant issues they wish to present to a hospital administrator. An actual hospital administrator serves as a facilitator in enacting role plays with the residents. Discussion focuses on effective negotiating styles, responses to authority, and socialization differences between physicians and administrators that affect their interactions.

On the last afternoon, chief residents participate in the Hollow Square Exercise.[19] In this "game," small groups are assigned roles and given a complex task to complete in competition with each other within a limited time. Observers note the effective and ineffective individual and group behaviors demonstrated as participants attempt to "win" by completing the task. A variety of constructive and detrimental behaviors emerge under these conditions. This provides an excellent opportunity for the group members to examine their personal contributions to effective and ineffective leadership and group behavior.

The final part of the afternoon is given to a review of the workshop experience, further discussion of "back-home" applications, and preparation for reentry into the residency environment. Attention is given to ensure that the experiences of the workshop are integrated into the residents' further professional development rather than left behind as 3 days isolated from the rest of their training. One technique, for example, is to have participants complete individual time capsules in which they list key learnings from the workshop. The learnings are then reinforced the following September when the facilitators mail back the time capsules. The workshop ends with the completion of written evaluation forms.

RESULTS

It is difficult to measure objectively the success of this workshop in training participants in leadership skills that improve their effectiveness as chief residents. First, it is difficult to quantify noncognitive learning and its contribution to performance of the chief resident's duties. Second, the duties vary from program to program and include such complex skills as giving feedback to other residents and managing conflicts involving house staff. It might be possible to compare data from residency programs that have sent a chief resident to the workshop with those that have not participated in the workshop or even to assign chief residents to experimental and control groups; but the multiple ways in which programs differ would preclude any significant conclusions about the effectiveness of the workshop alone as an intervention.

Nevertheless, despite the lack of quantifiable data from carefully controlled studies, there are several indicators that the course is valuable to participating chief residents and their residency programs. First, enrollment doubled from the first to the second year of the program. Also, more than two thirds of residency programs where a chief resident attends the workshop send a chief resident in subsequent years. This suggests that workshop attendance is seen as worth the investment in time and financial resources.

Ratings by the chief residents themselves on the end-of-workshop evaluation forms are presented in Table 2. They were asked to rate specific aspects of the course on a scale from 1 to 10, with 1 representing "poor/useless" and 10 representing "excellent/useful." The mean ratings given were 8.2 for the 1988 course, 7.6 for the 1989 course, and 8.9 for the 1990 course, for an overall weighted average rating of 8.2. When asked: "Do you believe this conference would be useful to other chief residents?" 97% of the respondents said yes, and most added comments such as: "Absolutely," "Every chief resident should attend," and "More than useful, it should be mandatory."

Table 2.—Mean Ratings of Chief Resident Training Program*

	1988 n=23	1989 n=47	1990 n=47
Introduction to conference: Johari window	7.4	6.6	8.2
Ice-breaker communication process	8.2	7.2	9.1
Task-process leadership instrument and discussion	7.4	7.3	8.7
Group process	8.4	8.0	8.1
Giving and receiving feedback	7.7	8.1	7.9
Hollow square exercise	7.6	7.2	9.3
Myers-Briggs type indicator	9.3	9.3	9.8
Conflict management skills	8.9	8.1	8.9
Conflict resolution process	9.2	7.6	9.1
Stress and stress management	7.0	6.0	N/A
Personal feedback process	9.2	7.3	N/A
Working with hospital administrators	8.3	7.1	9.1
Time capsule	8.4	7.1	9.3
Chief resident/program director role analysis	7.4	N/A	N/A
Mean ratings of all aspects	8.2	7.6	8.9

*Specific aspects of the course were rated on a 10-point scale (1, poor/useless; 10, excellent/useful); n indicates number of chief resident participants; and N/A, not offered in this workshop.

Twenty chief resident participants among the 67 attendees in 1988 and 1989 responded to a 6-month follow-up questionnaire asking them to comment on their experience as chief resident, those aspects of the course that have proved most useful, and any areas they think should be included or expanded on. Behaviors that individual respondents perceived to have been significantly modified as a result of the course included the following: insight into differences in personality types; improved ability to manage conflict; greater awareness of their personal strengths and weaknesses in leadership situations; greater ability to appreciate the perspectives of others; and improved ability to give negative feedback.

Finally, the questionnaire asked: "Any other comments about the course, questions, suggestions, etc." Ten of the 14 people who responded to that request specifically praised the course again, with comments such as the following: "I...feel that it was an invaluable experience and one which I will never forget," and "I have encouraged our future chief residents to go wholeheartedly."

COMMENT

The 1980s saw the development of a number of new initiatives to address the training of physicians in interpersonal skills—from courses on interviewing skills,[20-22] to Balint-type discussion groups,[23] to psychosocial support groups for medical students and resident physicians,[1,24] to resident retreats.[15] The Chief Resident Leadership Training Program addresses such training by applying theories and techniques from the field of organization development and management training to a group of individuals who are or who shortly will be in leadership roles in medicine and who will likely be in leadership roles in the future.

While other initiatives are designed to enhance physicians' interpersonal skills by broadening physicians' perspectives on the role of medicine in society,[25] minimizing the effects of stress during medical training,[15,25] improving communication with patients,[20-22] or teaching skills specific to middle managers,[26] this Chief Resident Training Program addresses another important aspect of current medical training and practice: awareness of personal leadership traits and the critical importance of teamwork—with fellow physicians, hospital administrators, other health care workers, and patients. Group interaction skills can be expected to have value in a myriad of other groups of which physicians are members. These groups include departments, committees, specialty groups, and others. Indeed, never before have physicians found themselves practicing in relation to so many different individuals and organizations, with all the attendant opportunities for collaboration and conflict.[2,11-13,27]

Judging from the evaluation forms and comments of workshop participants, this program successfully addresses the leadership training of residents making the transition to chief resident. Optimally, one would like a well-designed study demonstrating a positive effect on residency programs due to the improved efficiency, effectiveness, and job satisfaction of Chief Residents who have attended the workshop. However, such a study is difficult, perhaps impossible, to design. Yet there is no question that, subjectively, participants benefit from the course.

The importance of the leader in setting group norms and modeling behaviors has been well documented outside the field of medicine.[14,28,29] Presumably, similar principles apply to medical education: the benefits of having well-trained leaders in the role of pediatric chief resident are expected to "trickle down" to residents and medical students and affect their medical education process. Yet it is important that this course be placed in the context of overall organizational change.[3,11,30] It is hoped, therefore, that similar training programs can be developed for residents in other specialties, program directors, department chiefs, and others in significant leadership roles in medicine.

As medical education enters the next decade, a number of new strategies for training the physicians of the future are likely to unfold, of which the Pediatric Chief Resident Training Program is one. Training in the skills of human interaction, effective leadership, and teamwork may have a positive effect on the actual process of medical education and on ultimate satisfaction with the effectiveness of clinical practice as well.

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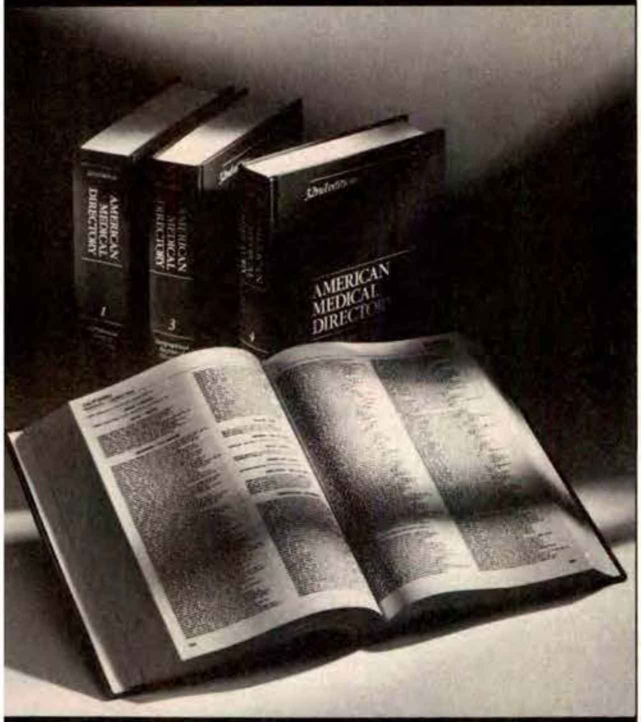

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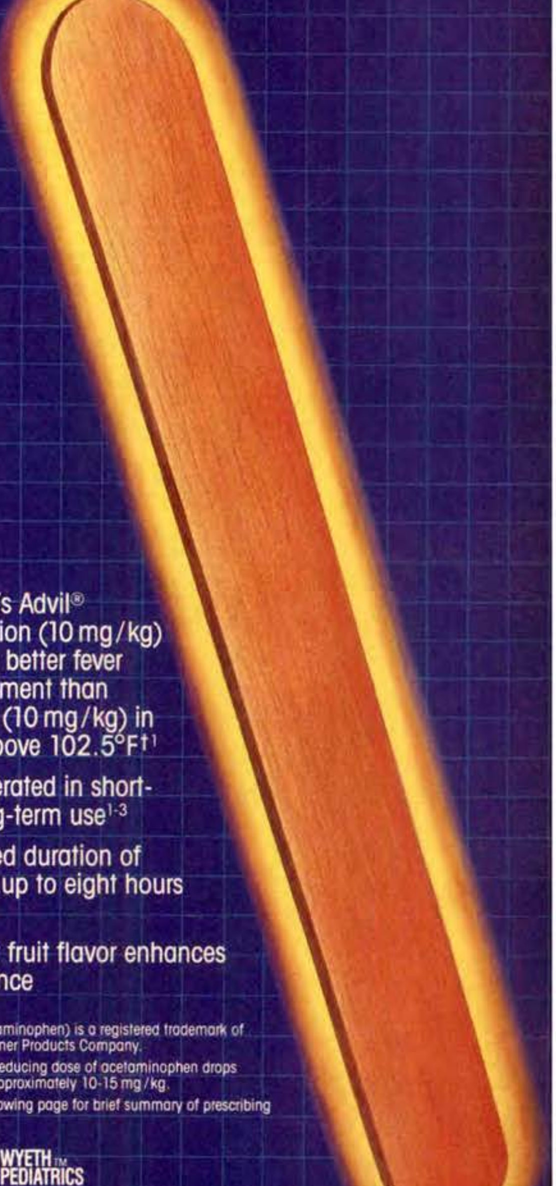

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WARNINGS: Risk of GI Ulcerations, Bleeding, and Perforation with NSAID Therapy: Physicians should remain alert for ulceration and bleeding in patients treated chronically with NSAIDS even in the absence of previous GI tract symptoms. In patients observed in clinical trials of several months' to two years' duration, symptomatic upper GI ulcers, gross bleeding or perforation appear to occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for one year.
Except for a prior history of serious GI events and other risk factors known to be associated with peptic ulcer disease, no risk factors have been associated with increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less well than other individuals and most spontaneous reports of fatal GI events are in this population.
PRECAUTIONS: General: Because serious GI tract ulceration and bleeding can occur without warning symptoms, physicians should follow chronically treated patients for the signs and symptoms of ulceration and bleeding.
Blurred and/or diminished vision, scotomata, and/or changes in color vision have been reported. If a patient develops such complaints the drug should be discontinued and the patient should have an ophthalmologic examination.
Fluid retention and edema have been reported with ibuprofen; therefore, the drug should be used with caution in patients with a history of cardiac decompensation or hypertension.
Ibuprofen can inhibit platelet aggregation and prolong bleeding time. CHILDREN'S ADVIL® SUSPENSION should be used with caution in persons with intrinsic coagulation defects and those on anticoagulant therapy.
The antipyretic and anti-inflammatory activity of ibuprofen may reduce fever and inflammation, thus diminishing their utility as diagnostic signs in detecting complications of presumed noninfectious, noninflammatory painful conditions.
Small decreases (usually not exceeding one gram) in hemoglobin and hematocrit with an apparent dose response relationship have been observed following chronic administration. If there are no signs of bleeding, it is probably not clinically important.
To avoid exacerbation of disease or adrenal insufficiency, patients on prolonged corticosteroid therapy should have their therapy tapered slowly when CHILDREN'S ADVIL® SUSPENSION is added to the treatment program.
Aseptic meningitis: Aseptic meningitis with fever and coma has been observed on rare occasions in adult patients on ibuprofen therapy. Although it is more likely to occur in patients with systemic lupus erythematosus and related connective tissue diseases, it has been reported in adult patients who do not have underlying chronic disease. If signs or symptoms of meningitis develop in a patient on CHILDREN'S ADVIL® SUSPENSION, the possibility of its being related to ibuprofen should be considered.
Renal Effects: As with other nonsteroidal anti-inflammatory drugs, long-term administration of ibuprofen to animals has resulted in renal papillary necrosis and other abnormal renal pathology. In humans, there have been reports of acute interstitial nephritis with hematuria, proteinuria, and occasionally nephrotic syndrome.
A second form of renal toxicity has been seen in patients with prerenal conditions leading to reduction in renal blood flow or blood volume. In these patients, administration of a nonsteroidal anti-inflammatory drug may cause a dose dependent reduction in prostaglandin formation and precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, and those taking diuretics and the elderly. Those patients at high risk who chronically take CHILDREN'S ADVIL® SUSPENSION should have renal function monitored if they have signs or symptoms of azotemia. Discontinuation of nonsteroidal anti-inflammatory drug therapy is typically followed by recovery to the pretreatment state.
Since ibuprofen is eliminated primarily by the kidneys, patients with significantly impaired renal function should be closely monitored and a reduction in dosage should be anticipated to avoid drug accumulation.
Information for Patients: Physicians may wish to discuss with their patients the potential risks and likely benefits of treatment with CHILDREN'S ADVIL® SUSPENSION.
Laboratory Tests: Meaningful (3 times the upper limit of normal) elevations of SGPT or SGOT (AST) occurred in controlled clinical trials in less than 1% of patients. A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of more severe hepatic reactions while on therapy with ibuprofen. If abnormal liver tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur, CHILDREN'S ADVIL® SUSPENSION should be discontinued.
Diabetes: Each 5 mL of CHILDREN'S ADVIL® SUSPENSION contains 2.5 g of sucrose which should be taken into consideration when treating patients with impaired glucose tolerance. It also contains 350 mg of sorbitol per 5 mL. Although in clinical trials CHILDREN'S ADVIL® SUSPENSION was not associated with more diarrhea than control treatments, should a patient develop diarrhea, the physician may wish to review the patient's dietary intake of sorbitol from other sources.
Drug Interactions: *Coumarin-type Anticoagulants:* Bleeding has been reported when ibuprofen and other nonsteroidal anti-inflammatory agents have been administered to patients on coumarin-type anticoagulants; the physician should be cautious when administering CHILDREN'S ADVIL® SUSPENSION to patients on anticoagulants.
Aspirin: Concurrent use of aspirin is not recommended.
Methotrexate: In vitro studies indicate that ibuprofen could enhance the toxicity of methotrexate. Caution should be used if CHILDREN'S ADVIL® SUSPENSION is administered concomitantly with methotrexate.
H_2 Antagonists: In studies with human volunteers, coadministration of cimetidine or ranitidine with ibuprofen had no substantive effect on ibuprofen serum concentrations.
Furosemide: Ibuprofen can reduce the natriuretic effect of furosemide and thiazides in some patients. During concomitant therapy with CHILDREN'S ADVIL® SUSPENSION, the patient should be observed closely for signs of renal failure as well as to assure diuretic efficacy.
Lithium: Ibuprofen produced an elevation of plasma lithium levels (15%) and a reduction in renal lithium clearance (19%) in a study of 11 normal volunteers during the period of concomitant drug administration. Patients should be observed carefully for signs of lithium toxicity. Read package insert for lithium before its use.
Pregnancy: Administration of ibuprofen is not recommended during pregnancy or for use by nursing mothers.
Infants: Safety and efficacy of CHILDREN'S ADVIL® SUSPENSION in children below the age of 12 months have not been established.
ADVERSE REACTIONS: The most frequent type of adverse reaction occurring with CHILDREN'S ADVIL® SUSPENSION is gastrointestinal. In clinical trials among adults involving chronic administration of ibuprofen, the percentage of patients reporting one or more gastrointestinal complaints ranged from 4% to 16%.
Incidence Greater Than 1% (but less than 3%), Probable Causal Relationship (see PRECAUTIONS): Abdominal cramps or pain, abdominal distress, constipation, diarrhea, epigastric pain,* fullness of the GI tract (bloating and flatulence), heartburn,* indigestion, nausea,* nausea and vomiting; dizziness,* headache, nervousness; pruritus, rash* (including maculopapular type); tinnitus; decreased appetite; edema, fluid retention (generally responds promptly to drug discontinuation).
Precise Incidence Unknown (but less than 1%), Probable Causal Relationship (see PRECAUTIONS): Abnormal liver function tests, gastric or duodenal ulcer with bleeding and/or perforation, gastritis, gastrointestinal hemorrhage, hepatitis, jaundice, melena, pancreatitis; alopecia, erythema multiforme, Stevens-Johnson syndrome, urticaria, vesiculobullous eruptions; aseptic meningitis with fever and coma, confusion, depression, emotional lability, insomnia, somnolence; amblyopia (blurred and/or diminished vision, scotomata and/or changes in color vision), hearing loss; agranulocytosis, aplastic anemia, decreases in hemoglobin and hematocrit, eosinophilia, hemolytic anemia (sometimes Coombs' positive), neutropenia, thrombocytopenia with or without purpura; congestive heart failure in patients with marginal cardiac function, elevated blood pressure, palpitations; anaphylaxis, bronchospasm (see CONTRAINDICATIONS), syndrome of abdominal pain, fever, chills, nausea and vomiting; acute renal failure in patients with pre-existing significantly impaired renal function, azotemia, cystitis, decreased creatinine clearance, hematuria, polyuria; dry eyes and mouth, gingival ulcers, rhinitis.
Precise Incidence Unknown (but less than 1%), Causal Relationship Unknown: Dream abnormalities, hallucinations, paresthesias, pseudotumor cerebri; photoallergic skin reactions, toxic epidermal necrolysis; cataracts, conjunctivitis, diplopia, optic neuritis; bleeding episodes (e.g., epistaxis, menorrhagia); acidosis, gynecomastia, hypoglycemic reactions; arrhythmias (sinus tachycardia, sinus bradycardia); angioedema, Henoch-Schönlein vasculitis, lupus erythematosus syndrome, serum sickness; renal papillary necrosis.
*Reactions occurring in 3% to 9% of adult patients treated with ibuprofen.
OVERDOSAGE: Patients with a history of ingestion of greater than 100 mg/kg should have induced emesis or gastric lavage. Multiple dose oral administration of activated charcoal may be useful. Supportive therapy may include oxygen, respiratory support, and parenteral fluids. Because the drug is acidic and excreted in the urine, administration of sodium bicarbonate and induction of diuresis may be beneficial.
DOSAGE AND ADMINISTRATION: Fever: 5 mg/kg if baseline temperature is 102.5°F or below or 10 mg/kg if baseline temperature is greater than 102.5°F, every 6-8 hours (children); 400 mg every 4-6 hours (adults).
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Article

Percentile Curves for Various Hematologic Measurements at Birth in Arab Preterm Babies of Different Gestational Ages

Khalid N. Haque, FRCP, DCH, Hassan M. Bahakim, MD

• Percentile curves were calculated for hemoglobin; hematocrit; total red and white blood cell counts; mean corpuscular volume; mean corpuscular hemoglobin; mean corpuscular hemoglobin concentration; and platelet, neutrophil, band cell, lymphocyte, monocyte, basophil, and eosinophil counts in preterm babies of 24 through 36 weeks' gestation. The curves were derived from mainly Saudi Arabian preterm babies who were born in Riyadh, which is just above sea level. Babies born to mothers with hematologic problems or babies who themselves had any evidence of hematologic disorder, blood loss, or disorders that affect hematologic values, eg, asphyxia, were excluded from the reference population. Six hundred two newborns were included in the study; however, after exclusions, the final reference population was 550. A minimum of 50 babies were studied for each gestational age except for gestations of 24 and 25 weeks. For these two gestations, 27 and 21 babies were studied, respectively. The percentile curves should be useful as a guide to the normal range of these variables in babies, particularly those of Arab origin.

(*AJDC.* 1991;145:645-649)

Although information concerning the normal values for various hematologic variables is abundant,[1-5] to our knowledge, very few studies have related these values to gestational age in premature babies.[5] This age group is of interest because values for most hematological variables undergo changes with gestational age. Moreover, extrapolation of normal limits available for children and infants may result in marked underestimation or overestimation.[6]

With increasing survival of smaller and smaller babies of shorter and shorter gestational age,[7,8] it has become important to establish normal hematologic values for these tiny babies. We report herein various hematologic variables in babies with gestational ages of 24 through 36 weeks.

PATIENTS AND METHODS

The study was conducted over a 6-year period from 1983 to 1989. During this period all babies born between 24 and 36 weeks' gestation were admitted to the Neonatal Intensive Care Unit (NICU) at King Khalid University Hospital, Riyadh, Saudi Arabia.

Gestational age was assessed by a combination of maternal dates, antenatal ultrasound examination, and postnatal gestational assessment done within 24 hours after birth using the Ballard[9] scoring system. Where there was a difference of more than 2 weeks between maternal dates and gestational assessment, the latter value was used. Babies were enrolled into the study if they were admitted to NICU with a gestational age of 24 through 36 weeks and if they and their mothers had no evidence of hematologic disorder, eg, antepartum hemorrhage, thrombocytopenia, or bleeding disorder. Babies who had conditions that could affect the hematologic[6] variables, eg, asphyxia, were also excluded from the study.

Every baby enrolled in the study had a 1-mL venous blood sample taken into an ethylenediaminetetraacetic acid tube for analysis of hematologic variables. The analysis was done on an automated blood cell counter (Coulter Counter S plus IV, Coulter Corp, Hialeah, Fla). Blood samples were taken between 4 and 6 hours after birth and differential cell count was done manually. No blood sample was drawn from either an umbilical vein or artery catheter.

During the period of study (October 1983 to October 1989) a total of 2050 babies were admitted to the NICU. Of those, 602 were eligible for enrollment into the study according to the criteria described above. Fifty-two babies were excluded later after developing disorders that would have affected their hematologic variables; a total of 550 babies were studied. All values thus obtained were analyzed on a personal computer (IBM, North Harbour, Portsmouth, England) using software from Statistical Analysis System (SAS Institute, Cary, NC). Scattergrams and percentile lines were also drawn using this program. To smooth out the curves a Harvard Graphics software program (Harvard Graphics Software Publishing Corp, Bracknell, England) also was used.

RESULTS

To make optimal use of our results we developed percentile grids for the following hematologic variables: hemoglobin and hematocrit; red blood cell count; white blood cell count; and platelet, neutrophil, band cell, lymphocyte, eosinophil, basophil, and monocyte count. These are presented in Figs 1 through 11. Although other percentile lines were also derived, for clarity of presentation only the 5th, 50th, and 95th percentiles are shown in the Figures. The absolute values for mean corpuscular

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From the Department of Pediatrics, College of Medicine, Riyadh, Saudi Arabia. Dr Haque is now with Chase Farm Hospital, Enfield, England.

Reprint requests to Department of Paediatrics, Chase Farm Hospital, The Ridgeway, Enfield EN2 8JL, England (Dr Haque).

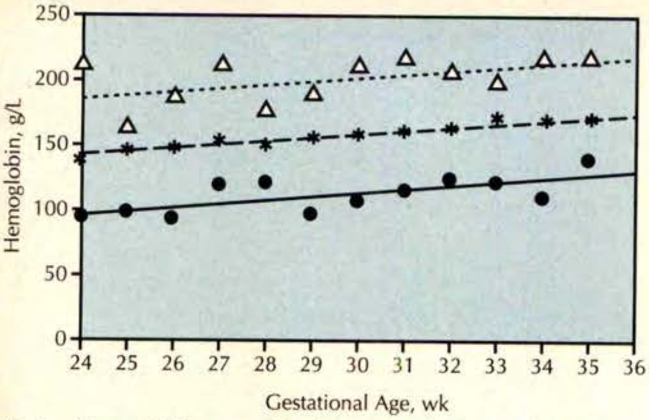


Fig 1.—*Hemoglobin percentiles in preterm babies. Solid line represents 5th percentile; dashed line, 50th percentile; and dotted line, 95th percentile.*

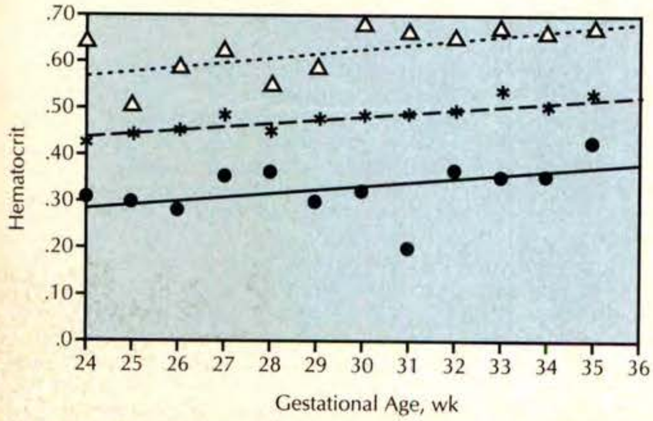


Fig 2.—*Hematocrit percentiles in preterm babies. Solid line represents 5th percentile; dashed line, 50th percentile; and dotted line, 95th percentile.*

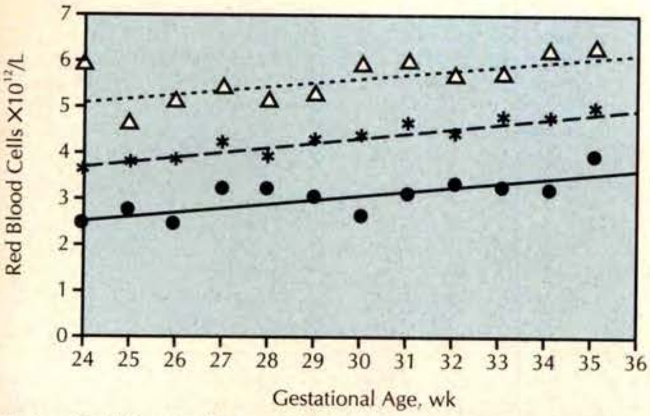


Fig 3.— *Red blood cell percentiles in preterm babies. Solid line represents 5th percentile; dashed line, 50th percentile, and dotted line, 95th percentile.*

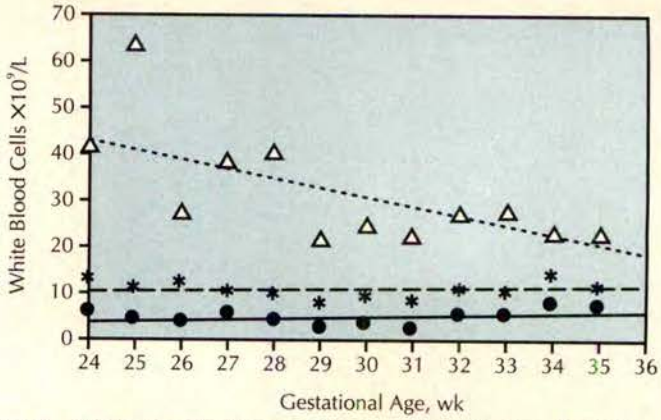


Fig 4.—*White blood cell percentiles in preterm babies. Solid line represents 5th percentile; dashed line, 50th percentile; and dotted line, 95th percentile.*

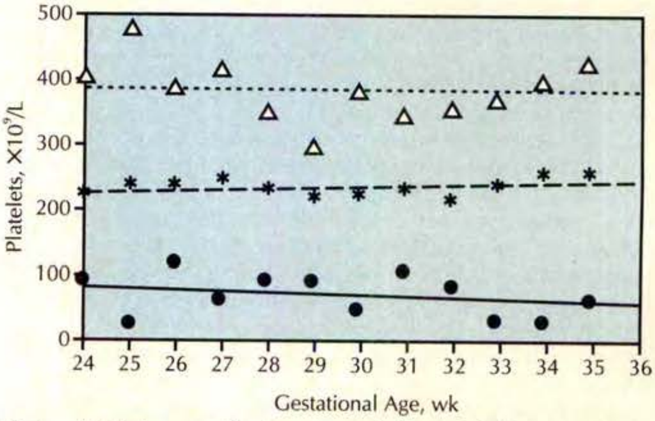


Fig 5.—*Platelet percentiles in preterm babies. Solid line represents 5th percentile; dashed line, 50th percentile; and dotted line, 95th percentile.*

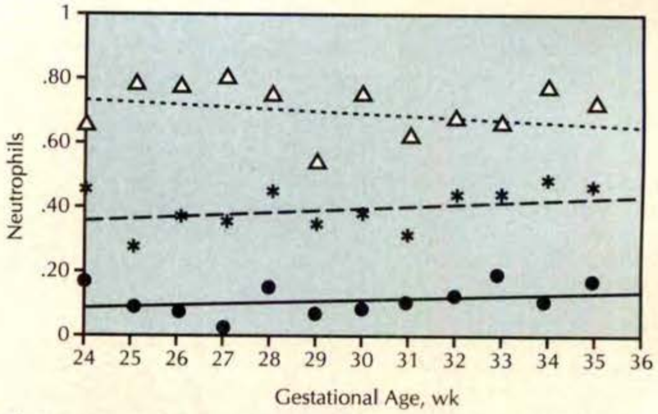
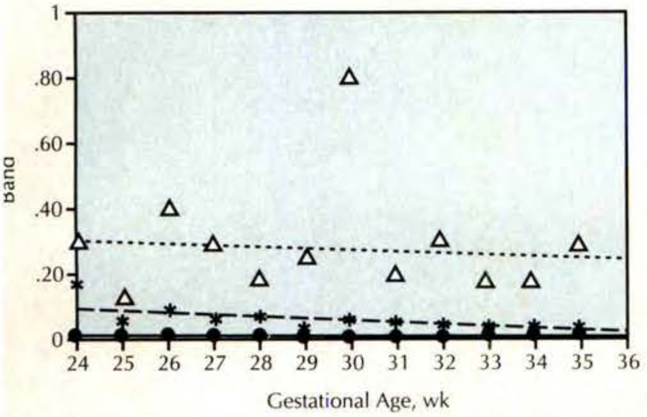


Fig 6.—*Neutrophil percentiles in preterm babies. Solid line represents 5th percentile; dashed line, 50th percentile; and dotted line, 95th percentile.*



ig 7.—*Band cell percentiles in preterm babies. Solid line represents th percentile; dashed line, 50th percentile; and dotted line, 5th percentile.*

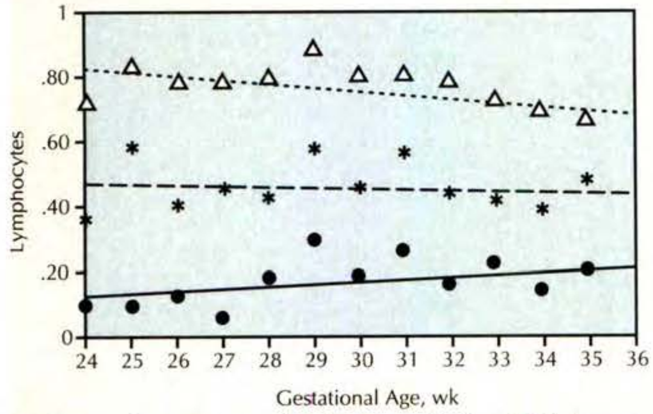


Fig 8.—*Lymphocyte percentiles in preterm babies. Solid line represents 5th percentile; dashed line, 50th percentile; and dotted line, 95th percentile.*

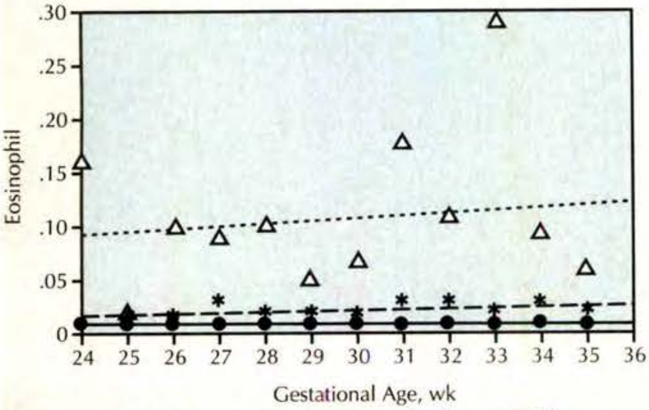


Fig 9.—*Eosinophil percentiles in preterm babies. Solid line represents 5th percentile; dashed line, 50th percentile; and dotted line, 95th percentile.*

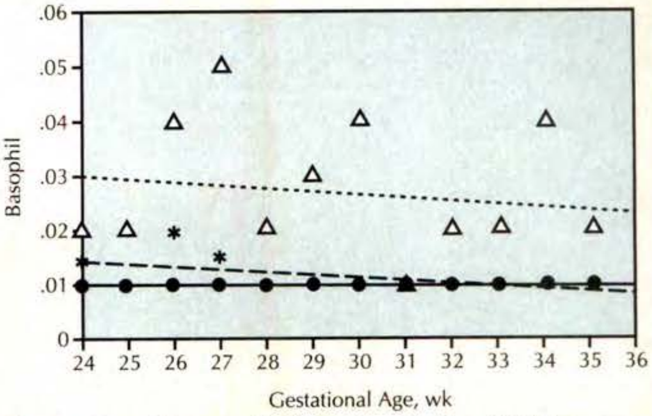


Fig 10.—*Basophil percentiles in preterm babies. Solid line represents 5th percentile; dashed line, 50th percentile; and dotted line, 95th percentile.*

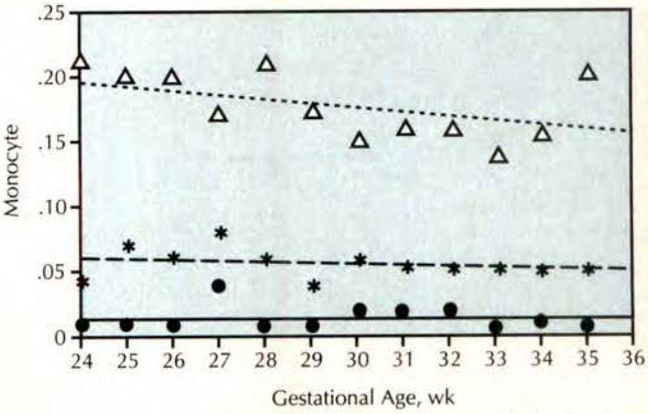


Fig 11.—*Monocyte percentiles in preterm babies. Solid line represents 5th percentile; dashed line, 50th percentile; and dotted line, 95th percentile.*

Table 1.—Absolute Values for Mean Corpuscular Volume Percentile in Preterm Babies

	Mean Corpuscular Volume Percentiles, fL		
Gestational Age, wk	**5th**	**50th**	**95th**
24	81	115.6	128.4
25	102.9	115.5	132.5
26	100.5	114.1	130
27	97.37	110.9	124.5
28	99.9	111.3	128.2
29	94.9	111.3	127
30	87.3	110.9	126.5
31	97	111.3	124
32	97.8	111.2	126.4
33	98.2	109.3	119.8
34	98.3	110.2	124.2
35	95.7	109.8	123.1
36	96.23	109.2	123.9

Table 2.—Absolute Values for Mean Corpuscular Hemoglobin Percentiles in Preterm Babies

	Mean Corpuscular Hemoglobin Percentiles, pg		
Gestational Age, wk	5th	50th	95th
24	26.6	38.5	43.7
25	33.6	38.5	42.2
26	31.12	37.6	42.5
27	31.1	37.6	42.5
28	33.15	37.7	43.62
29	33	37.2	41.2
30	30.7	36.9	41.1
31	32.15	36.1	41.6
32	32.1	37.6	42.7
33	31.5	36.6	39.84
34	31.4	36.8	40
35	33	36.3	41.7
36	32.08	36.3	41.29

Table 3.—Absolute Values for Mean Corpuscular Hemoglobin Concentration (MCHC) Percentiles in Preterm Babies

	MCHC Percentiles, g/L		
Gestational Age, wk	5th	50th	95th
24	306	337	354
25	324	331	346
26	315	331	350
27	313	332	370
28	321	333	352
29	315	332	358
30	318	333	349
31	312	331	348
32	320	337	362
33	312	331	350
34	311	333	348
35	316	334	355
36	321	332	351.6

volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration are given in Tables 1 through 3.

Of the 550 babies studied, mean birth weight was 1.9800 kg with a range of 480 to 3600 g. The gestational age was 24 through 36 weeks. The birth weight and length percentiles were similar to those described by Lubchenco et al.[10] A minimum of 50 babies were studied for each gestational age except for gestations of 24 and 25 weeks. For these two gestations, 27 and 21 babies were studied, respectively.

COMMENT

For establishing criteria of normality, two approaches are generally used. One commonly used and published in reporting growth standards uses the study by random sample of the total population.[11,12] The disadvantage of this method is that it does not include values of abnormal individuals. Inclusion of such individuals can be misleading if the curves are to be interpreted as representing normal standards.[1] The second method, and the one we chose to use, is to derive the normal data by excluding all subjects with evidence of common abnormalities (influencing variables) that might be expected to bias the data. Although this method has the disadvantage of excluding criteria that may seem arbitrary, it has certain advantages for the derivation of normative hematologic data.[1]

It is difficult to compare our values with earlier published data for the following two reasons: (1) we are not aware of any published data on hematologic values in preterm babies of Arab origin, and (2) previously published data from the Western literature[1,2,12-16] do not relate the values to gestational age. However, from a brief review of the literature,[4,5,13,15,17] it appears that the hematologic variables do not differ significantly between races, and these percentile charts may be applicable to non-Arab races as well. Monroe et al[5] have suggested that gestational age and birth weight do not affect neutrophil counts, but no data are available for other hematologic variables.

Comparison of our values with those published earlier[1,2,5,12-16] indicates that hemoglobin and hematocrit values are significantly higher than those reported by Dallman and Siimes,[1] and contrary to the findings of Monroe et al,[5] we found that gestational age has a significant effect on these two and other values (Figs 1 and 2; Tables 1 and 2).

Although our values of mean corpuscular volume and mean corpuscular hemoglobin (Tables 1 and 2) were similar to those reported by Dallman[13] and Saarinen and Siimes[2] in babies nearer full term, ie, 36 weeks' gestation, both these values were significantly higher in extremely premature babies of 24 to 25 weeks' gestation.

The red blood cell count (Fig 3) was much lower in the extremely premature babies but gradually rose to values similar to those reported in full-term infants[13] by 34 weeks' gestation.

Most interest has focused on the total white blood cell and the neutrophil counts because of their value in the diagnosis of sepsis. A wide range has been described (0.09 to 30 × 10^9/L) with a mean of 18.1 × 10^9/L by Dallman[13] and others.[15] The reason for this wide variation is that maternal conditions, eg, diabetes and hypertension, as well as the baby's condition, eg, asphyxia, respiratory distress syndrome, and hypoglycemia, influence the white blood cell count. In most studies, except for that by Monroe et al,[16] these variables have not been taken into account. We took them into account with our exclusion criteria, and our values (Fig 4; Table 2) show that the range narrows considerably with maturity of gestational age. In fact, of all the hematologic measurements studied by us, the greatest effect of gestational age was seen on the total white blood cell count. We have also studied the proportion of different cells contributing to the total white blood cell count. These are shown in Figs 6 through 11. Platelet count and mean corpuscular hemoglobin concentration are shown in Fig 5 and Table 3.

In establishing reference ranges, a balance must be achieved between sensitivity and specificity.[18] By studying a large number of babies of different gestational ages and by excluding those conditions in the mother and the baby that could affect the hematologic variables, we believe we have produced percentile charts that will provide a guide with 90% confidence of the normal ranges of these variables in healthy Arab babies within these gestational ages.

We thank Erum Shiekh, MD, research assistant, for her valuable help in collecting the data.

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Samuel Rosen, PhD; Elizabeth Kleinerman, MD
(*Arch Pathol Lab Med.* 1991;115:494-498)

Meconium for Drug Testing

Edward C. Maynard, MD; Louis P. Amoruso, PhD; William Oh, MD

• **Samples of meconium from 28 neonates born to women suspected of drug abuse were tested for drugs of abuse (ie, cocaine, morphine, codeine, and marijuana). In each case, testing of urine from the mother, the newborn, or both had been ordered by the attending physician because of suspected maternal drug abuse. Seventeen (61%) of 28 meconium samples tested positive; 28 (60%) of 47 urine samples were positive. Meconium test results were concordant with the results of maternal or newborn urine testing in 24 (86%) of the 28 cases. In three cases, meconium was positive for cocaine when newborn urine was negative; in one case, meconium was negative when maternal urine was positive for cocaine. Compared with the combination of maternal and newborn urine testing, meconium testing had an 82% positive predictive value (14/17) and a 91% negative predictive value (10/11). Collection of meconium is simpler and more reliable than collection of urine, and testing of meconium was easily incorporated into routine procedures at a busy commercial laboratory. Meconium is a useful sample for drug detection in newborns.**

(*AJDC.* 1991;145:650-652)

Maternal drug abuse carries considerable risk for injury to the mother and her fetus or neonate.[1,2] The detection and treatment of maternal drug abuse is an area of growing concern to those involved in perinatal care; laboratory tests to detect drugs of abuse are essential to this effort. Maternal self-report is often unreliable for detection of drug abuse[3,4]; even inquiry and testing based on broad indications of possible maternal drug use leave many cases undetected.[5] In addition, social service agencies often request confirmation of perinatal drug abuse by testing of urine from the newborn. However, urine collection in neonates may be difficult or delayed, impairing the ability to screen effectively for fetal drug exposure.[6]

Ostrea and colleagues[7] recently reported on use of meconium as a sample for drug detection in neonates born to drug-dependent mothers. Cocaine, morphine, or cannabinoid was detected in meconium from all 20 neonates tested and in urine from only seven of 19 neonates tested. We report our experience using a modification of the Ostrea et al[8] technique.

SUBJECTS AND METHODS

Meconium was collected during the first 2 days of life from 28 neonates. The meconium was scooped into a specimen cup from the surface of an absorbent diaper to minimize contamination with urine. In each case, the mother was suspected of active drug use by history or symptoms, or had had pregnancy complications associated with drug use (eg, premature rupture of membranes, premature labor, abruptio placentae, intrauterine growth retardation, or poor prenatal care). In each case, testing of urine for drugs had been ordered by the attending physician.

Meconium was refrigerated after collection and tested in a commercial laboratory within 24 hours (Clinical Science Laboratory Inc, Mansfield, Mass). The meconium sample (1 to 2 g) was diluted in 5 mL of normal saline, mixed by vortex for 20 seconds, and allowed to stand refrigerated for a minimum of 15 minutes. After centrifugation at 1200 to 1400*g* for 10 minutes, the supernatant was tested by radioimmunoassay using a commercial kit designed for drug detection in urine (Abuscreen, Roche Diagnostic Systems, Montclair, NJ). Preliminary studies showed no difference in drug detection when meconium was diluted with the acidified buffer supplied with the radioimmunoassay kit or with normal saline (pH 6.3 to 6.7).

Each meconium sample was tested for cocaine and benzoyl ecognine (a cocaine metabolite), morphine, codeine, and tetrahydrocannabinol. The cutoff for a positive test result was 300 ng/mL for cocaine–benzoyl ecognine, morphine, and codeine, as recommended by the National Institute on Drug Abuse, Bethesda, Md[9]; in our laboratory, these cutoff values gave no false results when known negative or positive samples of urine or meconium were tested. A positive cutoff of 100 ng/mL was used for tetrahydrocannabinol, because in our laboratory lower cutoff values were found to yield false-positive results in known negative samples of urine and meconium. When the radioactivity in a sample was less than 10% above or below the number of counts per minute in the positive control, the sample was called "borderline negative" or "borderline positive." Two cases with borderline positive results are treated as positive in the data analysis, and one borderline negative result is treated as negative.

Results of the meconium testing were reported only to the principal investigator and not recorded in the patient chart or used for any clinical purpose. The study was approved by the Research and Human Subjects Committee at Women and Infants Hospital, Providence, RI.

Maternal or newborn urine samples were assayed as routine samples in the same commercial laboratory by enzyme immunoassay, thin-layer chromatography, and gas chromatography–mass spectrography.

RESULTS

Drugs of abuse were detected in 17 (61%) of 28 meconium samples and 28 (60%) of 47 urine samples (15 of 21 maternal, 13 of 26 newborn; Table 1). In 21 cases, paired samples of meconium and maternal urine were tested; results were concordant in 19 cases (90%). In 26 cases, paired

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From the Department of Pediatrics, University of Massachusetts Medical School, Worcester (Dr Maynard); Clinical Science Laboratory Inc, Mansfield, Mass (Dr Amoruso); and Department of Pediatrics, Brown University, Providence, RI (Dr Oh).

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Reprints not available.

Table 1.—Results of Drug Testing*

Patient No.	Meconium	Newborn Urine	Maternal Urine
1	Cocaine	Cocaine	Cocaine
2	Cocaine	Cocaine	Cocaine
3	Cocaine	Cocaine	Cocaine
4	Cocaine	Cocaine	Cocaine
5	Cocaine	Cocaine	Cocaine
6	Cocaine	Cocaine	Cocaine
7	Cocaine	Cocaine	Cocaine
8	Cocaine	Cocaine	Cocaine
9	Cocaine	Cocaine	Cocaine
10	Cocaine	Cocaine	Cocaine
11	Cocaine	Cocaine	Cocaine
12	Cocaine	Cocaine	Cocaine
13	Cocaine, opiates	Cocaine	Cocaine, opiates
14	Cocaine	Negative	Negative
15	Cocaine†	Negative	. . .
16	Cocaine†	Negative	. . .
17	THC	. . .	THC
18	Negative‡	. . .	Cocaine
19	Negative	Negative	Negative
20	Negative	Negative	Negative
21	Negative	Negative	Negative
22	Negative	Negative	Negative
23	Negative	Negative	Negative
24	Negative	Negative	. . .
25	Negative	Negative	. . .
26	Negative	Negative	. . .
27	Negative	Negative	. . .
28	Negative	Negative	. . .

*THC indicates tetrahydrocannabinol. Cocaine includes cocaine metabolites; opiates, morphine and codeine.
†Borderline positive (<10% above positive control value).
‡Borderline negative (<10% below positive control value).

Table 2.—Drug Detection in Meconium vs Maternal or Newborn Urine

	Maternal/Newborn Urine	
	Positive*	Negative†
Meconium		
Positive	14	3
Negative	1	10

*One or both positive.
†Both negative, or one negative and one not done.

samples of meconium and newborn urine were tested; results were concordant in 22 cases (85%).

Meconium test results were concordant with the combination of maternal and newborn urine testing in 24 (86%) of 28 cases (Table 2). Meconium testing detected the same drugs found in maternal or newborn urine in 14 of 15 cases (sensitivity, 93%; 95% confidence interval [CI], 80% to 100%). Meconium testing was negative in 10 of 13 cases where urine testing was negative (specificity, 77%; CI, 65% to 89%). Meconium testing predicted a positive urine test in 14 of 17 cases (positive predictive value, 82%; CI, 73% to 91%) and predicted a negative urine test in 10 of 11 cases (negative predictive value, 91%; CI, 82% to 100%).

In five cases, part of the meconium sample was frozen at −20°C for 1 month, then retested. Results were identical with the initial testing in every case.

COMMENT

The data presented herein suggest that testing meconium from the newborn compares favorably with testing of maternal or newborn urine as a means of detecting perinatal drug abuse. Certainly, the ideal way to detect maternal drug abuse is by repeated questioning and testing of the mother during and after pregnancy. For practical reasons, however, detection of maternal drug abuse often relies on maternal and newborn urine testing at the time of delivery. While urine testing is not a "gold standard" for identification of perinatal drug abuse, it is appropriate to compare meconium testing with the results of concurrent urine testing when assessing the reliability of this method for drug detection.

Compared with the combination of maternal and newborn urine testing, meconium testing was 93% sensitive, with an 82% positive predictive value. This supports the conclusion of Ostrea et al[7] that testing of meconium is an adequately sensitive method of screening for maternal drug abuse near the time of delivery. Note as well, that the single false-negative meconium result in our series was "borderline negative," or within 10% of the positive control value. In the Ostrea et al series, though, all of the mothers were known to be active drug users, and every newborn had at least one positive meconium sample, so no conclusion about the specificity of meconium testing could be drawn. In our series, meconium testing had a specificity of 77% and negative predictive value of 91% compared with urine testing.

The low specificity of meconium testing in our series reflects three cases in which meconium was positive for cocaine but urine testing was negative. These three cases may represent examples of maternal cocaine use more than 48 hours before the time of delivery. Cocaine is rapidly metabolized and excreted by the kidney and is usually detectable in urine for only 1 to 2 days after use.[10] Urine testing will, therefore, reflect maternal cocaine use only if the most recent use occurred less than 2 days before delivery. Meconium, however, may serve as a repository of drug metabolites excreted in bile and retained in the fetal gut during a period of days to weeks before delivery[7]; further research is needed to evaluate this hypothesis.

An alternative possibility is that the three cases of positive meconium and negative urine represent false-positive results. Any positive screening test must be interpreted in the context of all the information available for a given patient; caution must be exercised before using a screening test to label a patient in a way that might be harmful.[11]

The technique of meconium testing described herein was easily incorporated into routine drug testing procedures in a busy commercial laboratory. The high degree of concordance between the meconium and urine test results supports the use of suspension in saline rather than acid extraction of the meconium sample, at least for detection of cocaine and opiates.

Since the period of this study, meconium testing by the method described herein has been made available as a routine clinical test at another hospital (The Medical Center–Memorial, Worcester, Mass), using the same commercial laboratory. During the first several months, results have supported the findings of this study. In 25 cases, maternal or newborn urine samples have been tested in addition to meconium. Meconium and urine samples were negative in 15 cases and positive for the same drugs in four cases. In one case, meconium and maternal urine tested positive for cocaine, while newborn urine was negative. In five cases, the quantity of newborn urine submitted was insufficient for drug testing; meconium was positive for cocaine in one of these newborns.

Such examples of insufficient urine collection emphasize that a major advantage of meconium is the ease of its collection, which may result in detection of cases of maternal drug abuse that are missed when collection of urine is delayed or unsuccessful. The fact that freezing the sample for up to 1 month did not alter meconium test results also suggests that meconium can be collected and stored for later testing in batch. Meconium testing may thus provide a practical means for assessing the prevalence of perinatal drug abuse in large populations. One such study has been reported, in which both maternal urine and newborn meconium were collected for anonymous drug testing.[12] During a 17-day period, maternal urine was collected during labor at 258 (61%) of 426 deliveries; meconium was collected from 367 (86%) of the newborns, demonstrating significantly greater success in collection of meconium ($P<.001$ by χ^2). The prevalence of perinatal cocaine abuse determined by meconium testing (1.6%) was lower than that estimated by maternal urine testing (3.9%),[13] but not significantly different.

Collection of meconium is simpler and more reliable than collection of urine; testing of meconium for drugs of abuse seems to be both sensitive and specific compared with maternal or newborn urine testing; and meconium testing is easily incorporated into routine procedures at a busy commercial laboratory. Meconium is a useful sample for detection of perinatal drug abuse and may be particularly useful for prevalence surveys in large populations.

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Access to Health Care in the United States

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Indigent Patient Care—Then and Now

Loring W. Pratt, MD
(*Arch Otolaryngol Head Neck Surg.* 1991;117:484-485)

Indigent Care—Now

Neil O. Ward, MD
(*Arch Otolaryngol Head Neck Surg.* 1991;117:486-487)

Access to Care—The Problem of the Uninsured and Underinsured: The View From Washington

Jerome C. Goldstein, MD
(*Arch Otolaryngol Head Neck Surg.* 1991;117:490-492)

Guidelines for Safe Transportation of Children in Wheelchairs

Kathleen M. DiGaudio, RN, MSN, PNP, Michael E. Msall, MD

• Advocacy efforts by health care professionals have prompted state legislative changes mandating the use of car seats and seat belts by children. These initiatives have greatly improved the level of safety in transportation of nonhandicapped children. Despite these positive changes, the transportation needs of nonambulatory children have not been addressed. In addition, implementation of Public Law 99-457 will result in larger numbers of young children with motor impairments requiring transportation to preschool early intervention programs. This study sought to describe how safely children in wheelchairs are transported. Observations of subjects were made as they were transported by their families or agencies at a residential summer camp, a preschool program for children with developmental disabilities, and a school for children with cerebral palsy. A safety score system was developed based on laboratory studies conducted on wheelchair restraint systems. This observation tool described the position of the wheelchair in the vehicle, the occupant restraint system, and the wheelchair restraint system. These structured observations revealed inadequate safety measures. Comparisons of safety scores of subjects transported by families with those transported by agencies were not found to have statistically significant differences. The findings of this study demonstrate a gap between minimal safety standards in wheelchair transportation and actual observed practices. In an effort to promote safe transportation practices of children regardless of their developmental differences, we present guidelines for health care providers for monitoring safe wheelchair practices in family, school, and community settings.

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Epidemiological data have demonstrated a reduction in the reported incidence of injuries in New Mexico,[1] California,[2] Washington,[3] Michigan,[4] and Tennessee[5] following passage of state child restraint laws. All 50 states had implemented mandatory child restraint laws by 1986. The percentage of restraint use by children tripled between 1974 (20%) and 1984 (60%). It is estimated that 26% of the fatalities that would have occurred in 1984 in children aged 0 to 4 years were prevented.[6]

In 1977, at the University of Michigan Highway Safety Research Institute, Benson and Schneider[7] evaluated the effectiveness of wheelchair restraint devices. This research demonstrated that wheelchairs and restraint systems could be designed to provide effective impact protection for children with disabilities when utilizing the basic safety concepts listed in Table 1. The goal of this study was to provide data that would assess the adherence to these basic safety concepts and to initiate guidelines for the safe transportation of children in wheelchairs.

SUBJECTS AND METHODS

Sample

The target population consisted of 63 nonambulatory subjects between the ages of 2 and 21 years. All subjects were transported in wheelchairs to and from agencies in western New York. Administrators at three sites serving developmentally disabled persons granted permission for data collection with the assurance of anonymity.

Setting

Data were collected at three sites in western New York. Site 1 was a United Cerebral Palsy Association day treatment program. Site 2 was a center for multiply handicapped children aged 2 to 5 years utilizing Association for the Severely Handicapped principles.[8] Site 3 was a summer camp for children with disabilities.

Data Collection

An observation checklist for categorizing and recording specific aspects of the method of transporting the subject in a wheelchair was developed (Table 2).[7] Reliability of the instrument was established by two trained observers in the summer of 1987 at the summer camp. Sidewalk observations of 12 subjects were made as the children boarded or departed the vehicle. Both observers were in 100% agreement on data collected on the 12 subjects. The observer did not interact with the subjects, nor was her purpose known to the subjects or bus personnel. Each safety variable was assigned a point value so a combined "safety score" could be assigned. The presence of minimal essential safety factors equaled a score of 10. The scores ranged from 0 (no safety measures observed) to 10 (essential safety factors observed).

Informal discussions with parents of handicapped subjects and agency personnel provided valuable information on transportation-related injuries, methods of reporting such incidents, and the difficulties encountered by families of handicapped subjects.

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From the School of Nursing (Ms DiGaudio), and the Division of Developmental Disabilities and Rehabilitation, Department of Pediatrics, School of Medicine and Biomedical Science (Dr Msall), State University of New York at Buffalo.

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Reprint requests to Children's Hospital of Buffalo, Robert Warner Rehabilitation Center, 936 Delaware Ave, Buffalo, NY 14209 (Dr Msall).

Table 1.—Safety Principles for Wheelchair Restraints*

1. Position of chair: forward or rear facing
2. Occupant restraint system: chest and lap belt system that attaches to side of vehicle
3. Wheelchair restraint system: tie down straps on all four wheels of chair that attach to wheelchair frame and anchor in floor of vehicle

*Modified from Benson and Schneider.[7]

Table 2.—Observation Checklist

	Score	
Category (Points)	**2**	**0**
Position of chair (2)	Backward Front facing	Side facing
Restraint belts (4)	Lap belt/buckle Chest or shoulder strap	Velcro None
Wheel restraints (4)	Tie-down strap Front Rear	Locking bar Front Rear

Table 3.—Safety Scores by Transporters*

	Score		
	<2	4	6
Agency (n=50)	76	22	2
Parent (n=13)	92.3	7.7	0

*Values are percentages. Maximum score observed was 6; mean was 1.10.

Table 4.—Safety Principles

Principle	No. (%)
1. Position of wheelchair	
Forward facing	11 (17.5)
Rear facing	0 (0)
2. Child restraint system	
Shoulder belts	0 (0)
Buckle lap belts	11 (17.5)
3. Wheelchair restraints	
Four tie-down straps	3 (4.8)

Statistical Analysis

Descriptive data analysis was performed by measurements of central tendency. Safety scores of the three agencies were analyzed by analysis of variance (ANOVA) using the SPSS-X computer program.[9] The safety of methods of transportation by different agencies was compared using the χ^2 statistic.

RESULTS

Data in Table 3 reveal that the sample of subjects in wheelchairs was not transported safely. The range of safety scores was 0 to 6, with a mean of 1.10. Of the 50 subjects transported by agencies, a safety score of less than 2 was assigned to 38 subjects (76%), a score of 4 to 11 subjects (22%), and a score of 6 to one subject (2%). Thirteen subjects were transported by families, with a safety score of less than 2 in 12 subjects (92%) and a score of 4 in one subject (7.7%).

Table 4 reveals the breakdown of scores by safety principle. The recommended position of forward facing was observed in 11 (17%) of the 63 subjects. None of the subjects observed were transported in a rear-facing position. Similarly, the recommended restraint systems on the wheelchairs were utilized by 11 subjects (17%). Wheelchair restraint systems were safe on only three wheelchairs (4.8%). These alarming statistics confirm that subjects in wheelchairs are not transported safely.

Data were compared to determine if a difference in the level of safety existed among agencies. The mean safety scores of site 1 (1.26), site 2 (1.81), and site 3 (2.0) were analyzed by one-way ANOVA. No significant differences existed ($F=1.139$, $P>.05$).

Cross-tabulation was used to compare the safety scores of subjects transported by families as opposed to agencies. Safety scores were dichotomized into two groups. Group 1 consisted of scores below 3, and group 2 included scores of 3 or more. In group 1, agencies transported 38 subjects and families transported 12 subjects. In group 2, agencies transported 12 subjects and a family transported one subject. Overall, 50 subjects (79.4%) had scores below 3, while 13 (20.6%) had scores of 3 or more.

Discussion with families and agency personnel revealed an absence of documented transportation-related injuries. In addition, no systematic standard reporting mechanism existed if such an event occurred. Last, parents were not aware of the variety of specialized car seats for the disabled or whether their nonambulatory child would be safely restrained by standard seat belts.

COMMENT

Our results demonstrate that subjects with developmental disabilities in wheelchairs are not transported safely. Our results are similar to those of Bull and colleagues,[10] who observed misuse of car seats in 75% of their observations of children without disabilities. Though much of our safety scoring system seems to be commonsensical, ongoing reinforcement of these safety principles required. Safety education should extend beyond parents to educational and developmental professionals serving persons with disabilities.

Car seat laws may have gaps leading to inconsistent protection for children. Legally acceptable exemptions pose significant risks in safe transportation of nondisabled children. For example, in Missouri the legislation applies only to cars registered in the state.[11] Similarly, North Carolina restricts coverage to drivers licensed in that state. In Wyoming, 27% of the children killed in accidents were transported in pickup trucks, which are exempt from legislation.[11]

Our results suggest that exempting children with disabilities from safe transportation guidelines places them at risk for accidents. In addition, children with developmental disabilities in wheelchairs often lack the balance skills or protective responses necessary to avoid injuries during routine swerving, let alone collisions. However, the lack of a standard reporting mechanism for transportation-related injuries of children with disabilities does not allow ongoing collection of data to estimate this risk better. We agree with recent prevention and policy analysis that recommends coding the cause of injury for all hospital discharge or emergency department events to have data for preliminary risk estimates.[12]

Policy Guidelines

In an effort to address the safety needs of all children regardless of motor disabilities, we suggest the following guidelines.

Health Care Professionals as Advocates.—Physicians, nurses, and therapists in schools, agencies serving the disabled, and medical centers have a role in advocating safer transportation practices for children. The initial car seat legislation in Tennessee was the result of advocacy efforts by Robert S. Sanders, MD, a pediatrician.[13] Child advocates can assist handicapped children and their families by increasing awareness of safe transportation practices as well as the means of instituting the needed public awareness.

Health Care Professional–School Collaboration.—Several mechanisms are available to health care professionals to promote optimal safety in transportation of developmentally disabled children in wheelchairs. Physicians, parents, and schools must explicitly specify transportation goals in a child's individual educational plan.[14] School nursing and therapy goals must include an assessment of safety of transportation for children in wheelchairs. School boards should be made aware of medicolegal liabilities that can ensue if injuries result from unsafe transportation practices. Contracts for bus companies can be contingent on provision of safe transportation. Similar medicolegal liabilities exist for bus companies providing services and can be used to promote change.

Uniform Reporting Standards.—Standard incident reports need to be developed for recording transportation-related injuries by agencies and schools. This provides a means of monitoring trends in the incidence of injuries in a standardized fashion. Such standardization would also facilitate data collection for needed ongoing research in this area.

Family Supports.—Decreasing families' burdens in transporting their handicapped children must be emphasized. Wisbeach and Holt[15] had previously described problems that families encounter during routine use of wheelchairs, including folding, lifting, and transferring the chair without the child. Families need to be informed of safety principles in wheelchair transportation when equipment is provided. Financial resources for families must be identified that will aid them in obtaining the safest wheelchairs, the best restraint systems, or both.

Formal Policy Statement by Relevant Professional Organizations.—In the past, policy statements by health care professional organizations such as the American Academy of Pediatrics have greatly influenced public policy in the areas of school bus safety, car seats, and specific services for developmentally disabled children.[16-20] These statements should be expanded to include children in wheelchairs transported in personal and agency vehicles. Such a statement can precipitate the awareness of and the support for critically needed policy changes.

Summary

Both Public Law 94-142 and Public Law 99-457 require greater community and educational services for children with disabilities.[21,22] The recently passed Americans With Disabilities Act of 1989 (Public Law 101-366) also emphasizes greater access to and participation of individuals of all ages with disabilities in the full fabric of community life.[23] A key role for pediatric health care professionals is to stress basic safety principles for children in wheelchairs and to assist families in ensuring safety and alternative mobility. By advocating basic safety practices in transportation, additional disabilities can be prevented and increased participation of the disabled in community and educational settings can occur. This will further expand the partnership among pediatric health care professionals, families, and schools.

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Osteochondrodysplasia in Fryns Syndrome

Matthew M. Kershisnik, MD; Catherine M. Craven, MD; A. L. Jung, MD;
John C. Carey, MD; A. S. Knisely, MD

• Various skeletal abnormalities have been identified in roentgenograms of persons with Fryns syndrome, but to our knowledge, no histopathologic description of bone or cartilage has been published. We describe disordered endochondral and intramembranous bone formation in a premature female infant with Fryns syndrome. This infant and a full sibling (ie, had same set of parents) with Fryns syndrome in addition exhibited delayed ossification of the basiocciput and of cervical vertebral bodies, also previously undescribed in Fryns syndrome. These findings expand the spectrum of Fryns syndrome to include osteochondrodysplasia.

(*AJDC.* 1991;145:656-660)

Fryns syndrome is a generally fatal autosomal recessive disorder of unknown pathogenesis manifested by a consistent pattern of multiple congenital anomalies such as abnormal facies, diaphragmatic hernia, and distal limb abnormalities, and, more irregularly, by other congenital defects such as axial skeletal abnormalities and malformations of the respiratory, cardiovascular, gastrointestinal, genitourinary, and central nervous systems.[1] Reported defects include cystic dysplasia of the kidneys,[1-4] hypoplastic and abnormally lobulated lungs,[1-4] Dandy-Walker malformation,[2,4,5] Purkinje and granular cell heterotopia,[1,6] agenesis of the corpus callosum,[1,5] and aganglionosis of the colon and ureters.[3] Reported roentgenographic skeletal abnormalities include broad medial ends of the clavicles[1,3]; shortness of long bones, broad ribs, and globularly formed ilium[3]; unusually thin ribs[4]; and abnormal rib-vertebral junctions.[2] To our knowledge, no histopathologic description of bone or cartilage in Fryns syndrome has been published.

We identified, by light microscopy, morphologic abnormalities in rib and humeral physeal osteochondrogenesis in a premature female infant with Fryns syndrome. Delayed ossification of the basiocciput and of cervical vertebral bodies was seen in roentgenograms both of this infant and, on review, of a full sibling (ie, had same set of parents); at autopsy 9 years previously, the sibling was found to have multiple congenital anomalies that on review were compatible with Fryns syndrome. We herein report our observations, which expand the spectrum of Fryns syndrome to include osteochondrodysplasia with delayed cervical vertebral body and basioccipital ossification.

PATIENT REPORT

A 1200-g female infant was delivered by cesarean section prematurely at 27 weeks' gestation following acute maternal vaginal hemorrhage secondary to placenta previa. The pregnancy had been complicated by polyhydramnios, which was identified during preoperative ultrasonography.

The family history included parental consanguinity (parents are third cousins once removed [Fig 1]). A female full sibling died of multiple congenital abnormalities 9 years earlier; no syndromic diagnosis was assigned clinically or at autopsy. Two male full siblings are phenotypically normal.

Apgar scores were 0, 5, and 7 at 1, 5, and 10 minutes, respectively. Crown to heel length was 41.5 cm, and occipitofrontal circumference was 24.0 cm. The infant was intubated and surfactant was administered. Craniofacial dysmorphism was present with narrow skull, hypertelorism, lower canthal folds, upturned nose, and broad mouth (Fig 2). The nipples were widely spaced. The cartilaginous portions of the inferior ribs were abnormally pliable. The thumbs were broad and digitalized. The distal phalanges were short, and the nails were hypoplastic (Fig 3). Flexion contractures were present at all distal interphalangeal joints. A right calcaneovalgus deformity was present. M-mode ultrasonic examination of the infant's heart revealed double outlet right ventricle with subaortic ventricular septal defect, thickened mitral valve, thickened pulmonary valve with abnormal motion, and patent ductus arteriosus with bidirectional flow. Abdominal and cranial ultrasonic examinations were normal. The placenta, membranes, and cord (three vessels) were grossly unremarkable. Fryns syndrome was diagnosed clinically. Severe hypoxemia and bradycardia led to death at 12 hours.

Cultured peripheral blood lymphocytes showed a normal 46,XX Giemsa-banded karyotype. Fascial fibroblasts from the infant (NIGMS GM 10879) and peripheral-blood lymphocytes from the parents (NIGMS GM 10930 [mother], NIGMS GM 10931 [father]) were cultured and banked (NIGMS Mutant Cell Repository, Coriell Institute for Medical Research, Camden, NJ).

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From the Departments of Pathology (Drs Kershisnik, Craven, and Knisely) and Pediatrics (Drs Jung and Carey), University of Utah Medical Center, Salt Lake City.

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Reprint requests to Department of Pathology, University of Utah Medical Center, 50 N Medical Dr, Salt Lake City, UT 84132 (Dr Knisely).

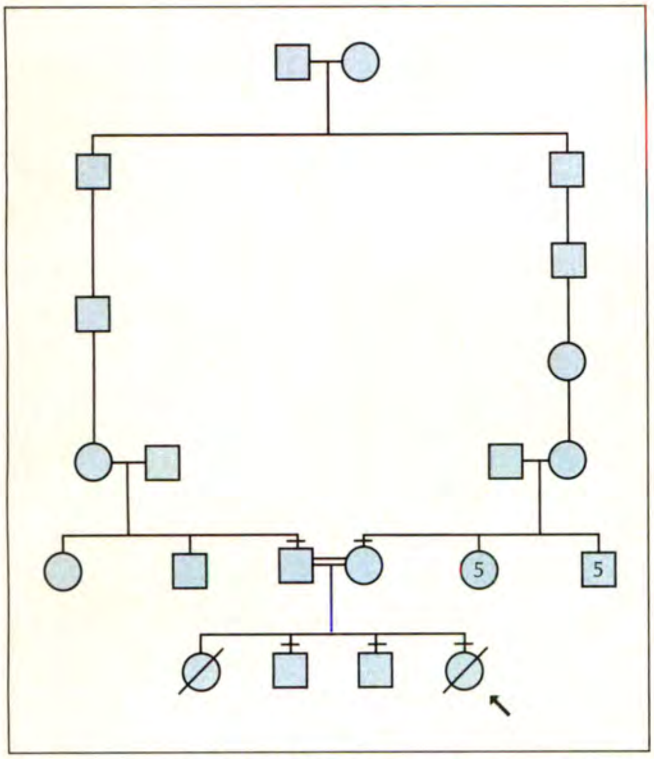

Fig 1.—*Family tree of kindred reported. Arrow indicates proposita; parents are third cousins once removed.*

At autopsy, external examination confirmed the antemortem findings. No disproportionate shortening of the extremities was noted. Asymmetric toe-heel lengths were 4.9 and 5.2 cm (expected,[7] 4.7 to 5.7 cm), and bilateral ulnar deviation of the hands at the radiocarpal joints was also noted. The inner canthal distance was 2.1 cm (expected,[7] 1.3 to 1.8 cm). The intercommissural distance was 2.9 cm (expected,[7] 1.6 to 2.2 cm). Postmortem roentgenograms showed broadening of the medial ends of the clavicles and delayed ossification of cervical vertebral bodies and basiocciput (Fig 4, top and bottom).

On internal examination, a 1.3 × 1.0-cm left posterolateral membranomuscular diaphragmatic defect was found, with displacement of the spleen into the left thoracic cavity. Clear ascitic fluid (20 mL) and bilateral pleural effusions (8 mL total) were present. The lungs were hypoplastic (combined weight, 11.8 g; expected,[7] 27.0±7.0 g [mean±2 SDs]) with failure of fissure formation between upper and middle lobes of the right lung. Cardiovascular findings included a persistent left superior vena cava with cardiomegaly (13.2 g; expected,[7] 9±5 g), a 0.2 × 0.3-cm membranomuscular ventricular septal defect, an abnormally thickened pulmonic valve cusp, agenesis of the nonseptal mitral papillary muscle, and a patent ductus arteriosus. Hepatosplenomegaly was present (liver and spleen weights, 101.5 and 6.0 g, respectively; expected,[7] 60±16 and 3±3 g, respectively). The genitourinary tract was normal with the exception of a uterus bicornis unicollis. The cerebrum, cerebellum, brain stem, and spinal cord were small but externally normal (brain weight, 100 g; expected, 180±53 g[7]). The cervical spine and cord were removed en bloc and serially transversely sectioned at levels inclusive of C-2 through C-6, corresponding to the innervation of the upper extremities; the cord and the brachial plexuses were grossly normal.

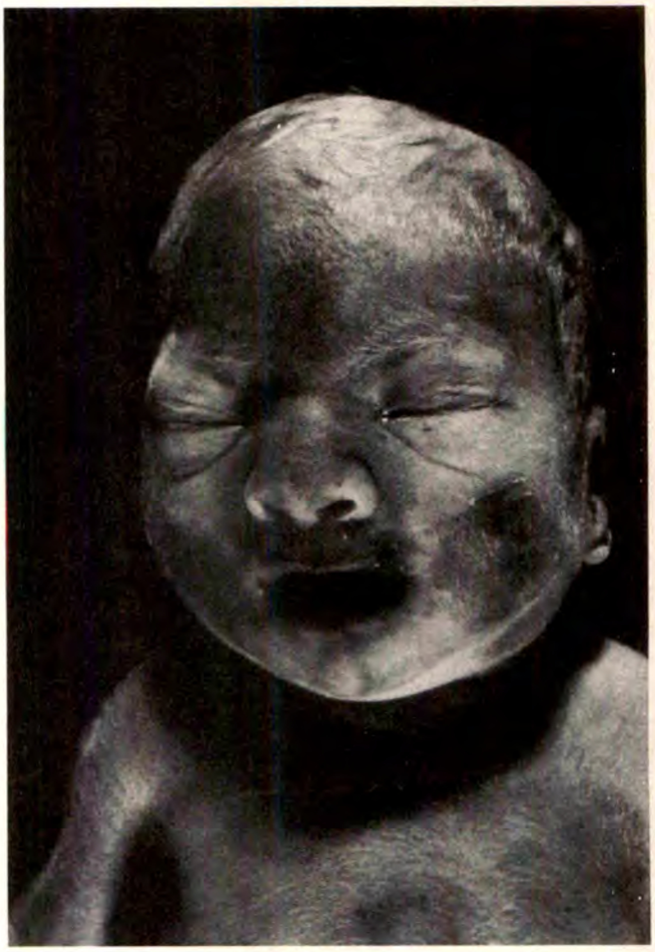

Fig 2.—*Face of younger sibling with Fryns syndrome. There is hypertelorism, the nasal tip is upturned, and the mouth is broad.*

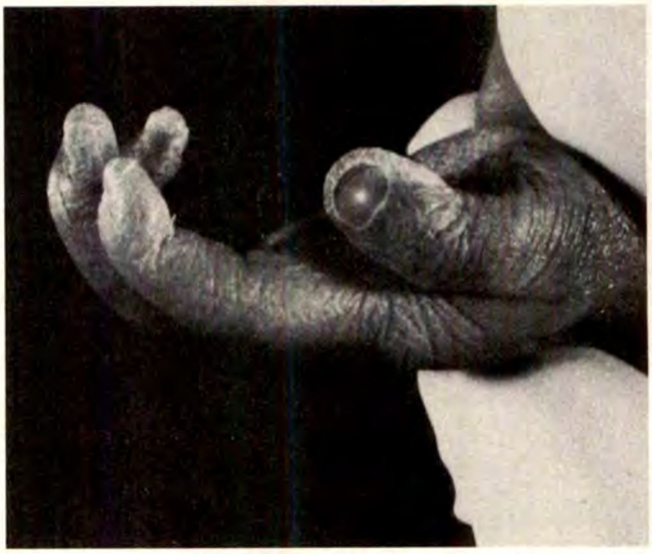

Fig 3.—*Hand of younger sibling with Fryns syndrome. There are flexion contractures of the distal interphalangeal joints. The distal phalanges are hypoplastic.*

On microscopy, bilateral acute pneumonia with hyaline membrane disease was present. The hepatic sinusoids and splenic red pulp were congested. The glomeruli and renal tubules were normal. Myenteric neural elements were present in the colon. An ectopic focus of poorly organized Purkinje and granular cells within inferior cerebellar white-matter tracts was identified. All other organs were

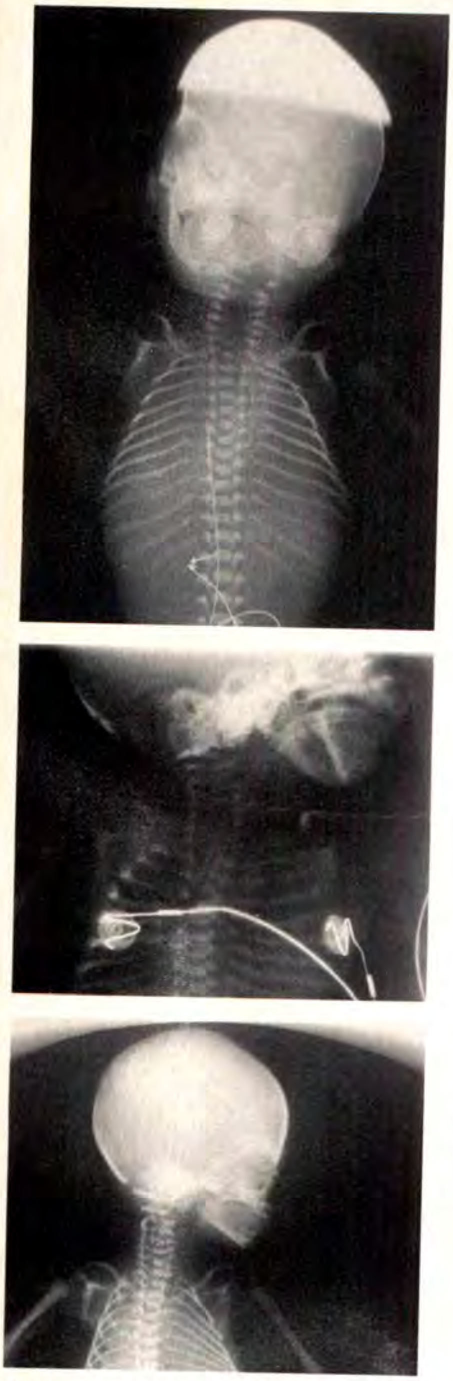

Fig 4.—*Top, Roentgenogram of younger sibling with Fryns syndrome (gestational age, 27 weeks). The medial aspects of the clavicles are broadened, and the basiocciput and the bodies of the first through sixth cervical vertebrae are not mineralized. Center, Roentgenogram of older sibling with Fryns syndrome (gestational age, 28 weeks). The medial ends of the clavicles are broadened, and the basiocciput and the cervical vertebral bodies are not mineralized. Bottom, Roentgenogram of infant without Fryns syndrome (gestational age, 25 weeks). The medial ends of the clavicles are slender. The basiocciput and the cervical vertebrae are clearly mineralized.*

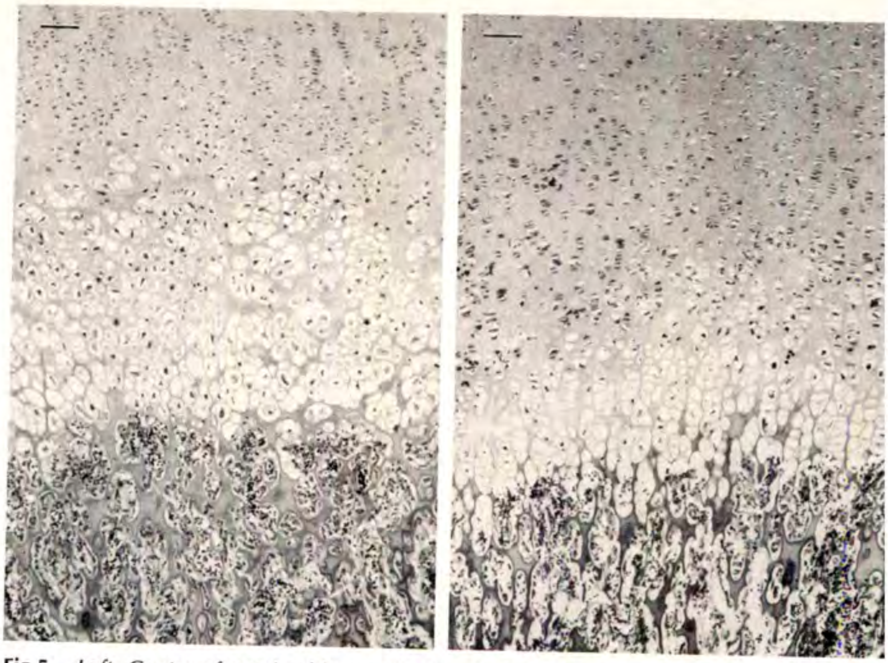

Fig 5.—*Left, Center of proximal humeral physeal plate of younger sibling with Fryns syndrome. Chondrocyte columnarization in the zones of proliferation and hypertrophy are markedly disorganized (hematoxylin-eosin, original magnification ×100; bar=100 μm). Right, Center of proximal humeral physeal plate of age-matched comparison infant without osteochondrodysplasia. Compare with Fig 5, left (hematoxylin-eosin, original magnification ×100; bar=100 μm).*

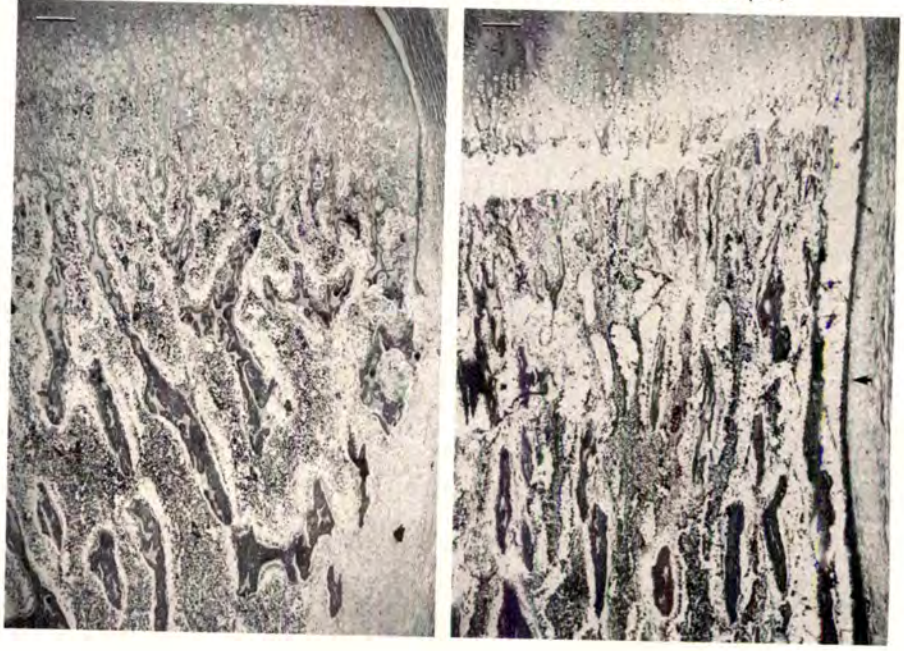

Fig 6.—*Left, Margin of proximal humeral physis of younger sibling with Fryns syndrome. Metaphyseal trabeculae are coarse and thickened. Subperiosteal bone is discontinuous and the periosteum is thickened (arrow) (hematoxylin-eosin, original magnification ×100; bar=200 μm). Right, Margin of proximal humeral physis of age-matched control infant without osteochondrodysplasia. Trabeculae are slender; subperiosteal bone is delicate and continuous (arrow) (hematoxylin-eosin, original magnification ×50; bar=200 μm).*

unremarkable microscopically with the exceptions of the cervical vertebral, anterior costal, and proximal humeral physes (see below). The diagnosis of Fryns syndrome was supported by the characteristic dysmorphic features, diaphragmatic hernia, and cardiovascular, pulmonary, and genitourinary system abnormalities.

Patient Report of Sibling

Clinical, roentgenographic, and autopsy records, including glass slides, for the deceased full sibling were reviewed. The infant, an 1190-g girl, was prematurely born (28 weeks' gestation) and died 5.5 hours after delivery. A Giemsa-banded karyotype was 46,XX. External abnormalities included an abnormal face with suborbital creases, micrognathia, low-set ears, and mild neck webbing; bilateral clinodactyly and flexion contractures of distal interphalangeal joints of hands with deep palmar creases; bilateral flexion contractures of knees; bilateral club feet; and omphalocele. Internal abnormalities included a ventricular septal defect; incomplete rotation of the bowel with infrahepatic cecum; agenesis of the corpus callosum; and Dandy-Walker malformation. Diaphragmatic hernia was not seen. Broadening of the medial clavicles and delayed cervical vertebral body and basioccipital ossification were identified on review of antemortem roentgenograms (Fig 4, center and bottom). Bone and cartilage had not been sampled for histologic examination; abnormalities were not identified in other tissues by microscopy. The diagnosis of Fryns syndrome was retrospectively assigned.

Bone Histologic Features

Longitudinal sections of proximal humeral and anterior costal physes of the younger sibling and age-matched controls without apparent osteochondrodysplasia were stained with the following: hematoxylin-eosin; periodic acid–Schiff with and without diastase digestion; Masson's trichrome; toluidine blue O; and alcian blue at a pH of 1.8, with and without hyaluronidase digestion, using conventional techniques.[8] In hematoxylin-eosin–stained sections, the Fryns cartilage, by comparison with that of the age-matched controls, contained poorly oriented columns of chondrocytes and strands of matrix in physeal zones 1 and 2 (zones of hypertrophy and proliferation, respectively). Columns of chondrocytes were crowded and irregularly shaped (Fig 5, left). In age-matched controls, chondrocyte columnarization and strands of matrix in zones 1 and 2 were longitudinally oriented and organized (Fig 5, right).[9,10]

The central bony trabeculae of the Fryns metaphysis were coarse and thickened, and they generally lacked longitudinal orientation (Fig 6, left). The control metaphyses were strikingly different. They contained delicate, thin, homogeneous, generally longitudinally oriented bony trabeculae (Fig 6, right).

The metaphyseal periosteum of the infant with Fryns syndrome was abnormally thickened. The subperiosteal bone was coarse and discontinuous; it did not extend to zone 1 at the lateral margins (Fig 6, left). Similar morphologic changes were identified in sections of cervical vertebral laminae of the infant with Fryns syndrome. In contrast, a distinctly continuous subperiosteal rim of bone extending to zone 1 at the lateral margins was present in the control metaphyses; the periosteum was thinner and did not envelop subperiosteal islands of trabecular bone (Fig 6, right). No histochemical differences between sections from the infant with Fryns syndrome and comparison sections were seen using special stains.

COMMENT

Fryns syndrome is an autosomal recessive disorder characterized by craniofacial anomalies, diaphragmatic hernia, and distal digital hypoplasia.[1,3,4,11] Relatively common conditions that may be confused with Fryns syndrome include trisomy 18 (Edwards' syndrome) and Robert's syndrome. Limb abnormalities readily distinguish Fryns syndrome from these syndromes. Patients with Edwards' syndrome show hypoplasia of the hallux and nails; patients with Robert's syndrome show phocomelia.[12] Neither syndrome manifests diffuse distal digital hypoplasia, which is characteristic of Fryns syndrome. Several other syndromes[12,13] also possess some of the anomalies seen in Fryns syndrome; however, each of these syndromic malformation patterns is different from that seen in Fryns syndrome.

The two patients we describe bring the total number of reported cases of Fryns syndrome to 35. They represent the fourth and fifth cases involving parental consanguinity,[6,11,14] the 10th instance of familial recurrence,[1-4,14,15] and the 25th and 26th confirmed cases of patients with normal karyotypes.[1,5] (Tandem duplication and ring chromosome abnormalities have been recently reported in patients with some features of Fryns syndrome[16,17] who are not considered cases of Fryns syndrome in this article.) The older sibling represents the fourth case of a patient with Dandy-Walker malformation[2,4,5] and the third case of a patient with callosal agenesis.[1,5]

Previously identified roentgenographic abnormalities in patients with Fryns syndrome include the following: bifid manubrial ossification centers[1]; broad medial ends of the clavicles; shortness of the long bones, broad ribs, and globularly formed ilium[3,6]; unusually thin ribs[4]; and abnormal rib-vertebral junctions.[2] Both infants described here had broadened medial ends of the clavicles and delayed cervical vertebral body and basioccipital ossification; their skeletons were otherwise grossly and roentgenographically unremarkable. The observed skeletal abnormalities are presumed manifestations of the genetic defect(s). These findings, in conjunction with previous case reports, suggest partial expression of a short limb dwarfism.[3]

Histologic sections of bone from the youngest sibling showed disordered endochondral and intramembranous bone formation. Chondrocyte columnarization was disorganized, metaphyseal bone was irregular and coarse, metaphyseal periosteum was thickened, and subperiosteal intramembranous bone formation was discontinuous. The observed histopathologic abnormalities in endochondral and intramembranous bone formation were most striking in the proximal humeral physis. The anterior costal physis showed similar histopathologic changes; however, the changes were more subtle than those seen in the proximal humeral physis. Disordered intramembranous (subperiosteal) ossification is characteristic of some osteochondrodysplasias (fibrochondrogenesis, thanatophoric dysplasia[18]) and has been reported in oto-palato-digital syndrome, type II.[19] While abnormalities in endochondral ossification have been identified at autopsy in 60% of infants of less than 32 weeks' gestation,[20] these have not been associated with frank skeletal malformation or heritable syndromic disease, but rather with intrauterine growth retardation. Neither sibling was small for gestational age. Accordingly, our findings indicate osteochondrodysplasia rather than nonspecific intrauterine growth retardation.

On microscopic review of sections of an anterior costal physis from an infant with Fryns syndrome whose case had been reported previously,[1] we found no abnormalities. This suggests that osteochondrodysplasia may not be a consistent finding in Fryns syndrome or that histopathologic changes may be better appreciated in the appendicular skeleton (proximal humeral physes). Future investigations of patients with Fryns syndrome should include histologic examination of bony physes[8] obtained either at autopsy or at diaphragmatic herniorrhaphy.

Many new and superficially unrelated abnormalities have been described in patients with Fryns syndrome[1-5,11,15-17,21,22] since its initial recognition.[13] This report adds osteochondrodysplasia to the spectrum of associated defects, suggesting that the responsible gene affects skeletal development as well as body wall, cardiovascular, genitourinary, and central nervous system organogenesis. Our studies of these two siblings provide new roentgenographic (delayed basiocciput and cervical vertebral body ossification) and histopathologic evidence of osteochondrodysplasia as a feature of Fryns syndrome.

C. Richard Nixon, MD, Department of Medical Imagery at Primary Children's Medical Center, Salt Lake City, Utah, assisted in interpreting the roentgenograms; Kurt Benirschke, MD, Department of Pathology, University of California at San Diego, provided access to sections of rib from the infant with Fryns syndrome whose case was previously reported; and Susan L. Wall, MT(ASCP), and her staff provided technical assistance.

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Autosomal Recessive Lethal Infantile Cytochrome C Oxidase Deficiency

Gideon Eshel, MD; Eliezer Lahat, MD; Kalman Fried, MD, PhD; Josef Barr, MD; Varda Barash, MD; Alisa Gutman, MD; Salvatore DiMauro, MD; Mordechei Aladjem, MD

• Three bedouin children with mitochondrial myopathy due to cytochrome c oxidase deficiency presented with progressive muscle weakness, failure to thrive, proximal renal tubular acidosis, and lactic acidemia leading to death. Two died by age 5 months and one by age 16 months. Cytochrome c oxidase was markedly reduced in skeletal muscle extracts of all three. Three other children of the same family with most probably the same metabolic aberration are also described. We suggest an autosomal recessive inheritance for this lethal mitochondrial myopathy.

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Biochemical abnormalities of mitochondria may affect lipid or pyruvate metabolism, the respiratory chain, or the coupling of respiration and phosphorylation.[1] The concept of mitochondrial myopathy was introduced by Luft et al[2] in 1962 and was based on morphological and biochemical abnormalities of muscle mitochondria in a patient whose clinical manifestations could be explained by the mitochondrial dysfunction. In the past decade, clinical and biochemical investigations have led to the identification of several specific errors of mitochondrial metabolism and the current classification of mitochondrial myopathies based on primary biochemical defects.[1] A defect of the respiratory chain affecting cytochrome *c* oxidase (COX) was described in a baby with generalized weakness from birth, severe lactic acidosis, and a renal disorder similar to de Toni-Fanconi-Debré syndrome. The child died of respiratory failure at age 13 weeks.[3] Since this original description, 10 patients with the same clinical and biochemical syndrome have been reported.[4-9] Most of the patients died before age 4 months. In their families, autosomal recessive inheritance appeared likely because twin sisters of one patient[3] and the brother of another[6] died in infancy with similar symptoms, and two patients were siblings.[7]

We describe a bedouin family with three children who had COX deficiency and three who presented with clinical and laboratory findings highly suggestive of the deficiency. This highly inbred family is large enough to provide conclusive evidence of an autosomal recessive mode of inheritance for this disorder.

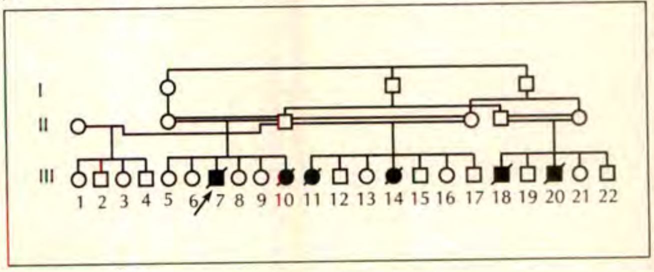
PATIENT REPORTS

The father of four of these children was polygamous and married to two first cousins and to an unrelated woman, all of whom were healthy. The family pedigree is presented in Fig 1.

Patient III-7 (Proband).—A 5-month-old boy was admitted with respiratory distress and hypothermia. He had been delivered after a full-term, uneventful pregnancy. Birth weight was 2100 g. Prior to hospitalization, several episodes of diarrhea and vomiting were noted. Feeding problems started immediately after birth. On admission, he weighed 2170 g, was severely dehydrated and floppy, and had a weak cry. Rectal temperature was 34°C, and respiratory rate was 60 beats per minute. Tendon reflexes were decreased symmetrically. Chest roentgenograms were normal. Measurements of arterial blood gases showed partially compensated metabolic acidosis with pH 7.30, a P_{CO_2} level of 19 mm Hg, P_{O_2} level of 70 mm Hg, and base excess level of −13 mmol/L. Additional levels were as follows: serum lactate, 4.0 mmol/L (normal, <2.0 mmol/L); serum pyruvate, 148 μmol/L (normal, <114 μmol/L); blood ammonia, 44 μmol/L (normal, 47 to 64 μmol/L); and plasma glucose, 4.8 mmol/L (normal, 3.85 to 6.05 mmol/L). No organic acids were found in the urine. On urinalysis, proteinuria was +3, glycosuria was +3, and generalized aminoaciduria was present. An electroencephalogram showed generalized diffuse slowing of the background activity, and a brain sonogram was normal. The child died 10 days after admission. A detailed autopsy was not performed, and only a skeletal muscle specimen was obtained from the vastus lateralis. The biochemical analysis of mitochondrial enzymes was performed by methods described elsewhere previously.[8] The results are presented in Table 1.

Patient III-10.—A 5-month-old girl presented with severe failure to thrive and had the following test values: serum lactate,

Fig 1.—*Family pedigree. Circles indicate females, and squares, males. The black squares and circles represent the clinically affected patients who are deceased. The arrow indicates the proband.*



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From the Pediatric Division (Drs Eshel, Lahat, Barr, and Aladjem) and Department of Genetics (Dr Fried), Assaf Harofeh Medical Center, Sackler School of Medicine, Tel Aviv, Israel; the Department of Clinical Biochemistry, Hadassah Medical Center, Jerusalem, Israel (Drs Barash and Gutman); and the Center for Muscular Dystrophy and Related Diseases, Columbia University, New York, NY (Dr DiMauro).

Reprint requests to Assaf Harofeh Medical Center, Zerifin 70300, Israel (Dr Eshel).

3.7 mmol/L; serum pyruvate, 136 μmol/L; blood ammonia, 56 μmol/L. She died of respiratory failure. Results of biochemical analysis of a muscle biopsy specimen obtained shortly before her death are shown in Table 1.

Patient III-20.—A 2-month-old boy was admitted because of prolonged diarrhea. He had been delivered after an uneventful pregnancy and weighed 3220 g. On admission, he weighed 3000 g; except for marked dehydration, results of physical examination were unremarkable. Laboratory examinations revealed metabolic acidosis with pH 7.27, $Paco_2$ level of 24.8 mm Hg, Pao_2 level of 65 mm Hg, and base excess level of −13 mmol/L. Test results included the following values: serum phosphate, 1.2 mmol/L; calcium, 2.24 mmol/L; serum lactate, 6.2 mmol/L; serum pyruvate, 132 μmol/L; blood ammonia, 62 μmol/L; and plasma glucose, 5.1 mmol/L. No organic acids were found in the urine, and serum carnitine levels were within normal limits. Urinalysis showed proteinuria, phosphaturia, glycosuria, and generalized aminoaciduria. Stool cultures were positive for *Salmonella*. The metabolic acidosis persisted, and oral treatment with bicarbonate, calcium lactate, and phosphate was begun. Starting at age 3 months, progressive diffuse hypotonia, gradual decrease in deep tendon reflexes, and increasing opsoclonus (involuntary eye movements) were noted. Electroencephalography revealed diffuse slowing of the background activit
Computed tomography showed diffuse cortical atrophy. The i
fant was readmitted several times following repeated episode
of bacterial infections until his death at age 16 months. Immu
nologic screening tests were normal. Muscle, heart, and brai
tissue were obtained after death for biochemical analysis. Th
results of analysis for mitochondrial enzymes are presented i
Table 1.

Patients III-11, III-14 and III-18.—Three additional sibling
and half-siblings of patients III-7, III-10, and III-20 presented a
ages of 1, 4, and 5 months with severe failure to thrive and pro
gressive hypotonia. Clinical and biochemical findings were ver
similar to those observed in patients III-7, III-10, and III-20 (Table
2 and 3). Proximal tubular dysfunction was diagnosed after lab
oratory findings disclosed proteinuria, glycosuria, and general
ized aminoaciduria. Computed tomography of patient III-1
showed diffuse cortical atrophy (Fig 2). The three children die
at ages 6, 15, and 23 months. Cytochrome *c* oxidase activity i
tissues was not examined.

COMMENT

The mitochondrial respiratory chain is divided into fou
functional units or complexes, each composed of severa

Table 1.—Mitochondrial Enzymes in Skeletal Muscles of Three Patients and in the Brain and Heart of Case III-20*

Tissue Type and Patient No.	COX	Succinate	NADH Cytochrome C Reductase	Succinate DH	NADH DH	CS
Muscle						
III-7	0.231	0.513	0.970	0.60	20.64	4.27
III-10	0.000	0.605	1.400	1.44	25.00	8.42
III-20	0.108	0.378	0.270	0.63	24.03	3.90
Controls (No.)	2.80±0.52 (71)	0.70±0.228 (68)	1.020±0.377 (78)	1.00±0.526 (78)	35.48±7.07 (76)	9.88±2.55 (73)
Brain						
III-20	0.486	0.432	0.217	0.406	12.10	6.176
Controls (No.)	0.517±0.168 (13)	0.336±0.228 (12)	0.640±0.240 (9)	1.920±0.500 (8)	9.29±2.54 (21)	6.05±1.77 (21)
Heart						
III-20	3.45	4.41	0.649	3.67	79.03	34.56
Controls (No.)	4.63±1.59 (10)	1.70±0.44 (9)	3.10±1.45 (7)	1.78±0.55 (7)	69.66±11.4 (7)	35.68±14.2 (7)

*All assays were carried out on crude extracts. COX indicates cytochrome *c* oxidase; NADH, rotenone-sensistive reduced nicotinamide-adenine dinucleotide; DH, dehydrogenase; and CS, citrate synthase. Enzyme values are in micromoles of substrate per minute per gram of tissue. Control values are means±SEMs.

Table 2.—Clinical and Biochemical Data of the Six Patients*

	Patient III-7	Patient III-10	Patient III-11	Patient III-14	Patient III-18	Patient III-20
Date of birth	12/21/83	5/20/81	1/16/77	7/22/80	10/10/80	5/23/83
Sex	M	F	F	F	M	M
Age at admission, mo	1	1	5	1	4	2
Age at death, mo	5	5	15	23	6	16
Birth weight, g	2100	2000	2500	3000	3500	3220
Death weight, g	2170	2650	4100	4600	4720	4610
Failure to thrive	+	+	+	+	+	+
Recurrent infections	+	−	+	−	+	+
Lactic acidosis	+	+	+	+	+	+
Renal tubular acidosis	+	+	+	+	+	+
COX deficiency	+	+	ND	ND	ND	+

*COX indicates cytochrome *c* oxidase, and ND, not done.

proteins that are embedded in the inner mitochondrial membrane. Complex IV (COX) is composed of 13 polypeptides. Subunits I, II, and III are transcribed by mitochondrial DNA, while the remaining 10 are encoded by nuclear DNA. Genetic errors affecting the nuclear-coded subunits may impair the assembly of the whole complex in muscle or other tissues and cause different clinical syndromes.[1,10]

Table 4 summarizes a tentative clinical classification of COX deficiency based on differential tissue involvement.[10]

Sixteen patients have been reported to have lethal in-

Table 3.—Neurologic Manifestations*

	Patient III-7	Patient III-10	Patient III-11	Patient III-14	Patient III-18	Patient III-20
Hypotonia	+	+	+	+	+	+
Psychomotor retardation	+	+	+	+	+	+
Convulsions	−	−	−	+	−	−
Opsoclonus	−	−	−	−	+	+
Optic atrophy	−	−	+	−	−	−
Abnormal EEG	+	+	+	+	ND	+
Abnormal CT	ND	+	ND	+	ND	+

*EEG indicates electroencephalogram; CT, computed tomogram; and ND, not done.

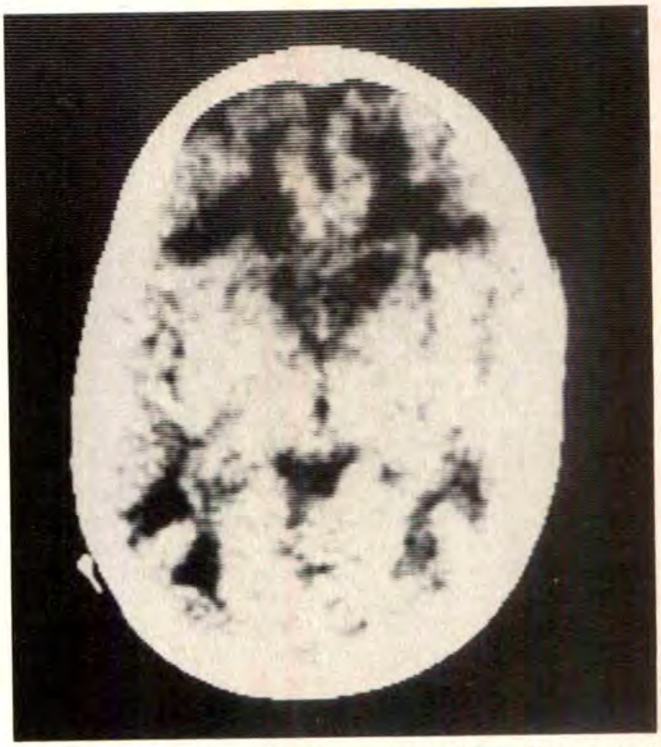

Fig 2.—*A computed tomogram of patient III-14 shows diffuse cortical atrophy with enlargement of the ventricular system.*

Table 4.—Cytochrome Oxidase Deficiency: Clinical and Laboratory Features

Clinical Syndromes	Reference No.	Myopathy	CNS Involvement*	Generalized Weakness	Hypotonia	Hyporeflexia	Respiratory Failure	Renal Tubular Acidosis	Cardiopathy	Liver Involvement	Lactic Acidosis
Syndromes dominated by muscle involvement											
Fatal infantile myopathy	7, 8, 11, 12	+	−	+	+	+	+	−	−	−	+
Fatal infantile myopathy and renal dysfunction	3-6, 13-15	+	+	+	+	+	+	+	−	−	+
Myopathy and cardiopathy	16-18	+	−	+	−	−	+	−	+	+	+
Myopathy and liver disease in second cousins	19	+	−	+	+	+	−	−	−	−	+
Benign infantile mitochondrial myopathy	20-21	+	−	+, reversible	+	+	−	−	−	−	+
Syndromes dominated by brain involvement											
Subacute necrotizing encephalomyelopathy (Leigh syndrome)	22-25	+	+	+	+	+	+	−	−	+	+
Progressive sclerosing poliodystrophy of children (Alper's disease)	26	−	+	−	−	−	+	−	−	+	−
Trichopol iodystrophy (Menkes' disease)	27	+	+	+	+	+	+	−	−	+	+

*CNS indicates central nervous system.

fantile myopathy.[3-9,11-18] Manifestations included generalized weakness, lactic acidosis, and de Toni-Fanconi-Debré syndrome. We add six patients with similar clinical and biochemical findings, three of whom had proven COX deficiency. This family enlarges our understanding of the spectrum of the natural history of COX deficiency. Our patients are different from those previously described in their longer survival and heterogeneous neurologic manifestations. Most of the other described patients died before age 4 months. All our patients survived for at least 5 months, the longest survival being 23 months.

In addition to generalized weakness, hypotonia, and hyporeflexia already reported in previous cases, our patients presented a variety of neurologic abnormalities, including severe psychomotor retardation in all affected children, seizure (one patient), optic atrophy (one patient), and opsoclonus (two patients). Electroencephalograms of five patients were abnormal, showing irregular slow background activity and irritative features in the patient with seizure activity. Computed tomography of the brain performed on three patients demonstrated diffuse cortical atrophy with enlarged ventricular systems. The possibility that our patients had variants of COX deficiency and Leigh syndrome[22-25] seems to us unlikely, since COX activity in the brain of patient III-20 was normal.

Autosomal recessive inheritance appeared likely in the families described previously in the literature. The large affected sibships in this highly inbred family prove the autosomal recessive mode of transmission.

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Tracking of Elevated Blood Pressure Values in Adolescent Athletes at 1-Year Follow-up

Jeffrey L. Tanji, MD

• Resting blood pressures were measured in 467 adolescents during preparticipation physical examinations for high school sports. Fifty-seven of the athletes (12.2%) had significantly elevated blood pressures. Forty-three (79.6%) of 54 subjects demonstrated significantly and persistently elevated blood pressures at 1-year follow-up. A family history of hypertension was positively associated with elevated blood pressures in 46 (80.7%) of 57 subjects compared with controls (23/410 [5.6%]). Consistent with previous studies, subjects with elevated blood pressures had a greater body weight (94.5±25.7 kg) compared with normotensive subjects (75.2±14.0 kg). Subjects with elevated blood pressures engaged in heavy resistance weight training (three times a week or more) more often (41/57 [71.9%]) than normotensive subjects (65/410 [15.8%]). These data support the idea that blood pressures measured during routine preparticipation physical examinations for high school sports are a useful tool in screening for elevated blood pressure in adolescents.

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Hypertension is a widespread condition affecting an estimated 58 million adults in the United States.[1] It is a proved risk factor for cardiovascular morbidity and mortality[2] and contributes to the leading cause of death in the adult American population.[3] Often, the diagnosis of hypertension is not made until the third or fourth decade of life, despite the hypothesis that borderline hypertension may exist before this for a long time. One of the obstacles in the early diagnosis of hypertension is the concept that many young adults, specifically adolescents, do not present as often for medical care compared with other age groups. An estimated 25 million adolescents participate regularly in organized sports.[4] Thirty-five states require an annual physician's examination before participating in organized sports at the high school and junior high school levels.[5] It is the hypothesis of this article that elevated blood pressures taken during the preparticipation sports physical examination correlate with elevated blood pressures at 1-year follow-up. This screening examination, therefore, may be useful in identifying a cohort at risk for the development of hypertension at a later date. Corollary findings from the project will ascertain if an association exists between elevated blood pressure and increased body weight and if an association exists between elevated blood pressure and regular weight training.

Longitudinal studies of children with blood pressures above the 95th percentile for age have revealed consistent tracking of elevated blood pressure, particularly in adolescent and obese subjects.[6] Previous studies have indicated that the single best correlate of elevated blood pressure is body mass.[6] The report of the Second Task Force on Blood Pressure Control in Children[7] has categorized significant hypertension as blood pressure persistently equal to or greater than the 95th percentile for age (≥142 mm Hg systolic and ≥92 mm Hg diastolic, group aged 16 to 18 years) and severe hypertension as blood pressure equal to or greater than the 99th percentile for age (≥150 mm Hg systolic and ≥98 mm Hg diastolic, group aged 16 to 18 years).

SUBJECTS AND METHODS

Subjects were 467 male and female adolescents (aged 15 to 19 years) who were enrolled in high school and required preparticipation physical examinations before their sports season. Included were all subjects who underwent screening examinations

Department Editors.—*William B. Strong, MD, Augusta, Ga; Carl L. Stanitski, MD, Pittsburgh, Pa; Ronald E. Smith, PhD; Seattle, Wash; Jack H. Wilmore, PhD, Austin, Tex*

Purpose.—*This section provides current information related to the medical needs of young athletes, as pertinent to counseling young athletes and their parents regarding sports participation and practices contributing to the health maintenance of the athlete, as well as current concepts in the prevention, diagnosis, and treatment of sports-related illnesses and injuries.*

Editorial Comment.—*This prospective study of blood pressure assessment of adolescent athletes addresses a common problem. It demonstrates the importance of medical follow-up and more aggressive evaluation of the youngster with elevated blood pressure. Family history, body size, the type of strength training in which the athlete participates, and the use of anabolic steroids are issues that need to be addressed.—W.B.S.*

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From the Department of Family Practice, University of California, Davis Medical Center, Sacramento.

Reprint requests to Department of Family Practice, University of California, Davis Medical Center, 2221 Stockton Blvd, Sacramento, CA 95817 (Dr Tanji).

from seven Sacramento (Calif) metropolitan high schools. Excluded were subjects who were absent on the days of the examination and students enrolled in their senior year of high school (for the purpose of tracking blood pressure more easily at 1-year follow-up). To decrease the possibility of selection bias, profiling of blood pressures was done for the excluded group (n = 113). No differences were noted compared with the study population.

All subjects underwent a screening history and physical examination, which was performed by five physician examiners according to a nationally published format.[4] The history included questions regarding current health status; symptoms; previous level of competition; and medical history, including trauma, surgeries, fractures, sprains, medications, allergies, and habits (ie, smoking, alcohol, recreational drugs). Specifically, a history of hypertension in first-degree relatives, history of loss of consciousness, palpitations, family history of heart disease or hypertension, and a cardiovascular review of systems were documented. The validity of the reported findings was strengthened by having a history questionnaire distributed 1 week before the examination for parental review and input. A history of weight training was elicited retrospectively by self-report from the participants; this was validated through the athletic coaching staffs by written survey.

The physical examination adhered to previously published standards[4] and included blood pressure determination using a manual sphygmomanometer according to American Heart Association criteria.[8] Cuff size selection, however, was not based on American Heart Association criteria for adults; rather, it was chosen using criteria for children and adolescents according to the Second Task Force on Blood Pressure Control in Children.[7] A cardiovascular examination, including auscultation of the heart and palpation of peripheral pulses, was included.

All findings were recorded using a standardized format,[4] which included the name of the subject's physician, home telephone number, sports, and high school. Criteria for an elevated blood pressure response were derived from the Report of the Second Task Force on Blood Pressure Control in Children[7] and used a blood pressure of 142 mm Hg or greater systolic or 92 mm Hg or greater diastolic as significant. All subjects with significant elevation in blood pressure according to these criteria were reported to the coach and school nurse after the examination for follow-up blood pressure checks within 3 months.

One year after the initial examination, 436 of the initial cohort of 467 (31 subjects were unavailable for follow-up) were examined again for their annual sports preparticipation physical examination. The same procedures as described previously were performed.

Statistical analysis was performed using a mean±SD value from the mean for descriptive data. A correlation coefficient analysis was used to analyze the relationship of elevated blood pressure between the two examinations. Student's paired *t* test was used to analyze differences between hypertensive and normal subjects. A χ^2 test was used to analyze categorical differences.

RESULTS

The study population consisted of 359 male and 108 female adolescents (mean age, 16.2±2.2 years; range, 15 to 19 years) who were enrolled in high school and participating in a school-organized sports team. The group included 289 white (61.9%), 73 black (15.6%), 59 Hispanic (12.6%), and 46 Asian (9.9%) subjects; this racial distribution was representative of the demographic characteristics of the seven high schools.

As might be expected, the study population was a generally healthy group, with the only prior hospitalizations being for orthopedic trauma (12 [2.6%]) and asthma exacerbation (two [0.4%]). Twenty (4.3%) of the cohort of 467 reported a history of an elevated blood pressure; none reported a history of using an antihypertensive medication or illnesses or complications as a result of elevated blood pressure.

At the initial evaluation, 57 of the subjects (12.2%) had significantly elevated (≥142 mm Hg systolic, ≥92 mm Hg diastolic) blood pressures according to the stated criteria.[7] Forty-eight (13.4%) of 359 men and nine (8.3%) of 108 women met these criteria. A family history of hypertension by self-report was present in 46 (80.7%) of the 57 subjects with significantly elevated blood pressures as opposed to 23 (5.6%) of 410 normal subjects. Subjects with elevated blood pressures had a greater body weight (94.5±25.7 kg) than normal subjects (75.2±14.0 kg; *P*<.05). Subjects with elevated blood pressures engaged in heavy resistance training (defined as three times a week or more), 41 (71.9%) of 57 to a greater frequency than normotensive subjects (65/410 [15.8%]; *P*<.5). Subjects with an elevated blood pressure did not demonstrate racially related patterns, as 31 (10.7%) of 289 white, nine (12.3%) of 73 black, eight (13.6%) of 59 Hispanic, and nine (19.6%) of 46 Asian subjects met the criteria for a significantly elevated blood pressure.

Blood Pressures of 436 High School Athletes at Initial Examination and Follow-up

Blood Pressure	Initial Examination	1-y Follow-up	*r* Value	
			Systolic	Diastolic
Normal	382	368	.77	.79
Elevated	54	43	.72	.74

At 1-year follow-up, of the original cohort of 467, 31 (6.6%) were unavailable for follow-up, leaving a group of 436, who were tracked longitudinally for the 1-year study. Three (9.7%) of the 31 subjects unavailable for follow-up met the criteria for a significantly elevated blood pressure. The group unavailable for follow-up did not differ significantly in blood pressure compared with the original study population. Of the group of 436 tracked at 1-year follow-up, 48 (11.0%) demonstrated a significantly elevated blood pressure. Forty-three (79.6%) of 54 subjects with an elevated blood pressure at the initial examination demonstrated a persistently elevated blood pressure at 1-year follow-up.

Three hundred eighty-two subjects of the group of 436 tracked at 1-year follow-up initially had a normal blood pressure. At 1-year follow-up, 368 (96.3%) of the 382 continued to have a normal blood pressure, and the remaining 14 (3.7%) manifested a significantly elevated blood pressure not noted on the initial screening. Eleven (20.4%) of the cohort of 54 had a significantly elevated blood pressure at the initial screening examination and had a normal blood pressure at 1-year follow-up (Table). For both systolic and diastolic pressures in subjects with normal and elevated blood pressures, all *r* values were greater than .7.

COMMENT

These data support the hypothesis that elevated blood pressures according to the Second Task Force on Blood Pressure Control in Children criteria[7] taken as a part of a routine preparticipation sports examination are positively related to persistently elevated blood pressures at 1-year follow-up. These findings reinforce the concept that stratification of blood pressures in relation to peer groups begins before adulthood.[6] A normal blood pressure at initial evaluation is correlated with normal blood pressures at 1-year follow-up.

The implications of this study are to validate the significance of elevated blood pressures during routine screening of the 25 million adolescents who participate in annual school sports competition. Closer observation of the elevated blood pressures by follow-up has been recommended previously.[7] These findings support such recommendations. Earlier detection of patients at risk for hypertension would theoretically imply that earlier evaluation and intervention and improved control of blood pressure could occur. The Joint National Committee on the Detection, Evaluation, and Treatment of Hypertension proposes clear guidelines to follow and treat such patients.[3]

A 3-month follow-up evaluation after an initially elevated blood pressure for mild or borderline hypertension is the currently recommended standard of care. A clinically relevant question that arises after the detection of an elevated blood pressure according to the task force criteria[7] is whether a young athlete should continue to participate in his or her chosen sport. The American Academy of Pediatrics has published specific guidelines for this decision,[9] and the recommendations have been discussed and supported in the literature.[10] Generally, an athlete with no symptoms or end-organ damage in the presence of significantly elevated blood pressure may be allowed to compete in sports as long as blood pressure is carefully tracked.

Limitations of this study include the use of the standard manual sphygmomanometer, which could account for observer bias and errors in measurement of blood pressure. The rationale for using such a device is that in practice, such devices are used routinely to determine blood pressures and constitute the standard for measurement. Observer bias was minimized by "blinding" the observer as to the result of the previous blood pressure measurement, and all subjects were randomized to be examined by a group of five examiners.

One can be critical of the fact that in this prospective, longitudinal cohort study, 6.6% of the subjects were unavailable for follow-up. Attrition was minimized by initially excluding senior students from the cohort, although data were collected in this group to demonstrate no difference between this group and the study population. We believe that 6.6% attrition is a reasonable figure in light of the general issue of high school attendance as well as migration away from school. Within the group unavailable for follow-up, no variance in blood pressures were noted between that group and the study population.

Selection bias is a valid issue in this study. The fact that the study population represents high school athletes probably selects for a more active, fit, and healthier group than a typical adolescent population. The practical avenue of the preparticipation sports physical examination facilitated data collection for this cohort. Realistically, this screening examination in many cases may very well be the only contact that a healthy adolescent has with the health care delivery system. The issue of cuff size leading to falsely elevated blood pressures in subjects with greater body mass was addressed by using the criteria from the Second Task Force on Blood Pressure in Children as the method for determining appropriate cuff size for subjects.[7]

Strengths of the study include the large study population (N = 467), the low percentage of attrition in the study group (6.6%), the detail of information gathered in the history and physical examination, and the fact that this was a longitudinal, prospective cohort study.

A confounding variable that merits discussion is the possibility that elevated blood pressures in adolescents with increased body weight who engage in weight training may be associated with the illicit use of anabolic steroids.[11] The prevalence of anabolic steroid use has been estimated to be as low as 6%[12] and as high as 10%[13] among high school and college athletes. An experimental study to analyze the effect of anabolic steroid use on blood pressure is not ethically viable at this point, and retrospective self-report studies are flawed by the possible issue of underreporting of illegal drug use. It is stimulating to note the relationship between elevated blood pressures in larger athletes who weight train, but it is by no means valid to conclude that a relationship with anabolic steroid use may exist.

Further studies would point to continued follow-up of this cohort in a prospective, longitudinal study to determine when the diagnosis of hypertension is made. This sort of study sets the stage for interventional trials with closer follow-up and perhaps the earlier use of nonpharmacologic therapy for this population.

Randy Armstrong, MD, Pat Browning, MD, Belinda Murphy, DO, Terry Wrobel, DO, and Don Yokoyama, MD, provided support in data collection, and Barbara Claire prepared the manuscript.

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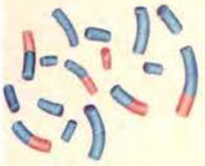

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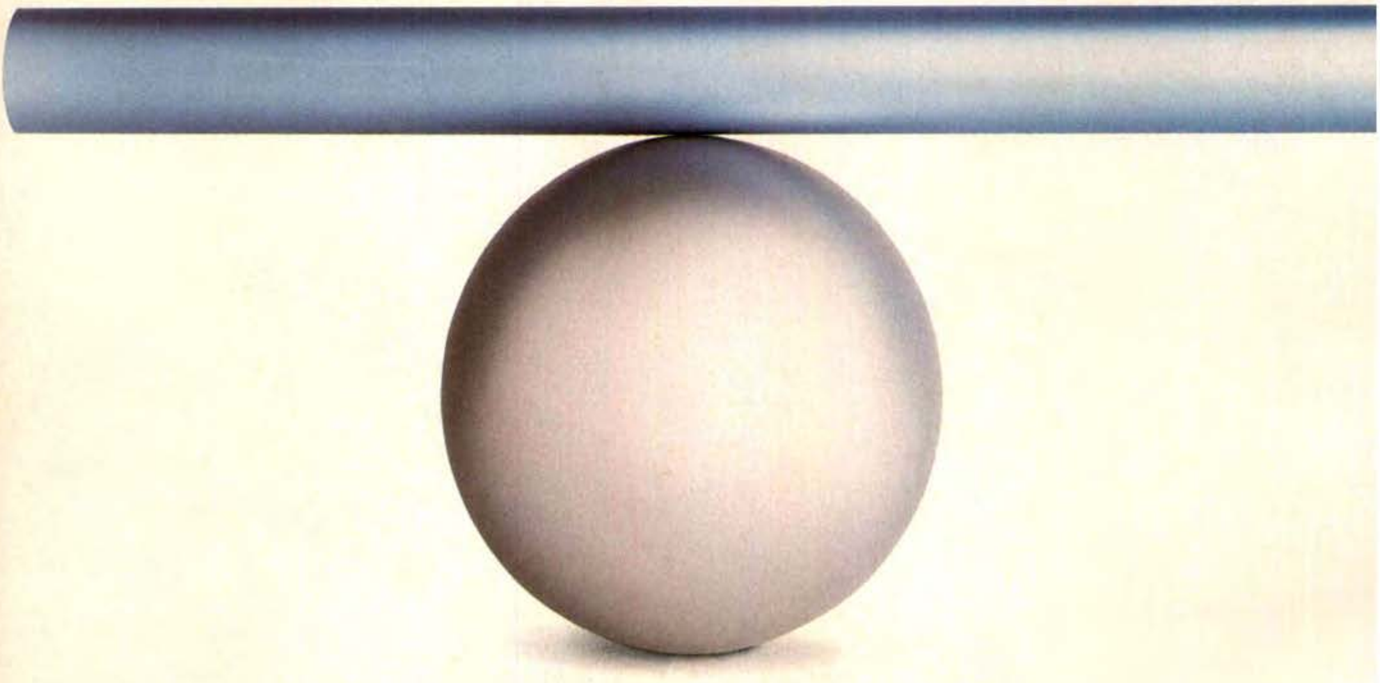

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Article

Escherichia coli Bacteremia in Children

A Review of 91 Cases in 10 Years

William A. Bonadio, MD; Douglas S. Smith, MD; Elisabeth Madagame, MD; Jane Machi, MD; Narendra Kini, MD

• We reviewed 91 cases of pediatric *Escherichia coli* bacteremia during a 10-year period. Thirty one patients were afebrile; a significantly greater proportion of these patients were aged less than 1 month, had ampicillin-resistant *E coli* isolates, or had persistent bacteremia 24 hours after initiating antibiotic therapy. Infection was community acquired in 65 cases; associated urinary tract infection was six times more common in this setting than in nosocomially acquired infections. In 85 cases at least 1 underlying medical condition/focus of infection was identified at the time the positive blood culture was obtained, the most common were immune deficiency states (38 cases), urinary tract infection (29 cases), and lesions of the gastrointestinal tract (27 cases). Polymicrobial bacteremia occurred in five cases. Twelve patients died; significantly associated with death were hypotension requiring pressor therapy, presence of a central venous catheter, and neutropenia.

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Escherichia coli is a gram-negative bacterium of the family Enterobacteriaceae, which has been shown to be a common cause of gram-negative sepsis in adults,[1,2] in children with underlying malignant neoplasms,[3,4] and in pediatric nosocomial infection.[3] *Escherichia coli* bacteremia in children is a potentially serious infection, as evidenced by the 60% associated mortality reported in one study.[3]

Information regarding pediatric *E coli* bacteremia is limited; most studies related to this infection have either examined specific patient populations[1,5] or described associated clinical characteristics within the larger context of gram-negative bacteremia.[2,3] We conducted a computer-assisted medical literature search of the past 20 years and were not able to identify a study that specifically described a large series of children with *E coli* bacteremia.

The purpose of this study was to delineate the clinical characteristics and outcomes of a large series of children with *E coli* bacteremia.

PATIENTS AND METHODS

We reviewed the results of consecutive blood cultures at Children's Hospital of Wisconsin, Milwaukee, from 1980 to 1990. Identified were instances in which the isolate was *E coli*. Microbiologic identification of these organisms was performed by standard methods.[6] Routine in vitro testing for susceptibility of isolates to a standard panel of antibiotics (which included ampicillin and gentamicin in all cases) was performed by means of the Kirby-Bauer disk method.[7] The medical records of all patients were reviewed, and all contained the following information: patient age/race/sex; underlying medical condition; current medications; symptoms; vital signs, physical findings, and results of laboratory tests performed at the time the positive blood culture was obtained; culture and sensitivity results; treatment received; subsequent clinical course; and outcome.

Fever was considered to have occurred when the body temperature was greater than 38.0°C during the 24-hour period of hospitalization before the original positive blood culture was obtained. Infection that occurred after 72 hours of hospitalization was considered nosocomially acquired. *Escherichia coli* bacteremia occurred when the organism was (1) the sole isolate from a single blood sample (both culture media) collected from a peripheral vein or artery when associated with an acute illness or (2) an isolate in two or more separate blood cultures when associated with another organism. Patients with *E coli* and a different organism isolated from a single blood culture were excluded from study unless these bacteriologic findings were confirmed by a subsequent blood culture (then consistent with polymicrobial bacteremia). Blood cultures positive for *E coli* obtained through a central venous or arterial catheter were considered consistent with bacteremia only if corroborated by an additional positive blood culture obtained from a peripheral vessel. Preceding antibiotic therapy was administered when a patient received parenteral antibiotics within 72 hours before the the initial positive blood culture was obtained. Persistent bacteremia occurred when *E coli* was isolated in two or more separate blood cultures obtained at least 24 hours apart. Neutropenia occurred when the peripheral absolute neutrophil count was less than 1.0×10^9/L. Death was associated with *E coli* bacteremia if it occurred while patients received treatment for this infection, unless clear clinical and pathologic data suggested otherwise.

The 11 variables analyzed included the following: mortality, presence of fever, presence of urinary tract infection, nosocomially acquired infection, hypotension requiring pressor therapy, presence of a central venous catheter, persistent bacteremia, isolate sensitivity to ampicillin, patient receiving care in an intensive care unit, preceding antibiotic therapy, and patient age less than 1 month. We chose the outcome variables to address the clinical questions of interest; they included mortality and presence of fever. Univariate analysis comparing these variables with all other variables was performed by means of χ^2 or Fisher's Exact Test where appropriate (the significant variables are given in Table 1). Many of these variables were not independent of one another. Spearman's correlation coefficients were determined along with *P* values for each correlation. Significant correlations

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From the Medical College of Wisconsin, Children's Hospital of Wisconsin, Milwaukee.

Reprint requests to 1240 Pioneer Trail, Waukesha, WI 53186 (Dr Bonadio).

Table 1.—Univariate Analysis*

Significant Variable	*P*
Mortality	
Hypotension requiring pressor therapy	.0015
Neutropenia	.016
Persistent bacteremia	.024
Presence of central venous catheter	.029
Nosocomial infection	.34
Preceding antibiotic therapy	.35
Fever	
Age<1 mo	.001
Ampicillin-resistant isolate	.001
Persistent bacteremia	.0039
Hypotension requiring pressor therapy	.012

*By χ^2 or Fisher's Exact Tests.

Table 2.—Spearman's Correlation Coefficients

Variables	Coefficient	*P*
Preceding antibiotic therapy/ nosocomial infection	.51168	.0001
Neutropenia/persistent bacteremia	.33819	.0010
Preceding antibiotic therapy/ persistent bacteremia	.30085	.0038
Preceding antibiotic therapy/ neutropenia	.22421	.0326
Central venous catheter/ nosocomial infection	.22404	.0328
Hypotension requiring pressor therapy/ age <1 mo	.21463	.0411

Table 3.—Stepwise Logistic Regression

Significant Variable	Odds Ratio	95% Confidence Interval
Mortality		
Hypotension requiring pressor therapy	14.45	2.80,74.44
Central venous catheter	14.89	1.70,130.64
Neutropenia	5.57	1.15,26.92
Fever		
Ampicillin-resistant isolate	9.17	2.61,32.17
Age <1 mo	0.10	0.029,0.35
Persistent bacteremia	14.64	2.15,99.56

Table 4.—Clinical Characteristics of Patients With *Escherichia coli* Bacteremia

Variable	No. of Patients
Patient age	
0-1 mo	33
1-2 mo	6
2-12 mo	18
1-5 y	10
5-10 y	4
10-18 y	20
Sex	
M	44
F	47
Race	
W	64
B	21
Hispanic	6
Abnormal clinical findings when positive blood culture obtained*	
Ill/toxic appearance	84
Fever	58
Respiratory rate >60/min	25
Heart rate >180 beats/min	24
Hypotension requiring pressor therapy	13†
Disseminated intravascular coagulation	10
Apnea	8
Nosocomial infection	26‡

*At least one finding was exhibited by each of the 91 patients.
†Seven aged less than 1 month.
‡Thirteen aged less than 12 months and eight aged 10 to 18 years.

among those variables significant in the univariate analysis are given in Table 2. Stepwise logistic regression analysis was then performed to control for this confounding; this analysis allows identification of variables that are independently significant after the effects of all others are controlled. These variables are given in Table 3 along with their odds ratios and 95% confidence intervals derived from the logistic coefficients and SEs.

RESULTS

During the study period, 4685 blood cultures were positive for bacterial isolates in 84 331 hospitalized patients. *Escherichia coli* accounted for 101 isolates (2%); 10 cases were eliminated from study because only a single positive blood culture yielded both *E coli* and at least one other organism.

There were 91 cases that met the study criteria for *E coli* bacteremia; their clinical characteristics are given in Table 4. The distribution of cases by season was 27 in spring (April through June), 29 in summer (July through September), 13 in autumn (October through December), and 22 in winter (January through March). All patients who survived at least 24 hours after the original positive blood culture was obtained had one or more additional blood culture performed. After the original positive blood culture was obtained and antibiotic therapy to which the organism exhibited in vitro sensitivity was initiated, 10 patients had persistent *E coli* bacteremia. The other isolates associated with the five cases of *E coli* polymicrobial bacteremia were *Enterobacter cloacae* (two cases), enterococcus, *Klebsiella pneumoniae*, and *Acinetobacter anitratus*; all five patients had persistent *E coli* bacteremia after antibiotic therapy to which the organism exhibited in vitro sensitivity was initiated, and one of these patients died. *Escherichia coli* isolates were sensitive to an aminoglycoside in all instances and to ampicillin in 62 instances; 29 isolates were resistant to ampicillin. Other sources of *E coli* isolates were urine (29 patients; 14 were aged <2 months and 27 had community-acquired infection), cerebrospinal fluid (eight patients; six were aged <1 month, four of whom were afebrile), indwelling central venous catheter (six patients), peritoneal fluid (seven patients), and abscess drainage (three patients).

The 117 underlying conditions/foci of infection identified at the time the original positive blood culture was obtained are given in Table 5. Of 20 patients aged 10 to 18 years, 15 had an immune deficiency, whereas five of 57 patients less than 12 months of age had a similar condition

Table 5.—Underlying Conditions/Foci of Infection Identified When the Original Positive Blood Culture for *Escherichia coli* Was Obtained

Condition/Foci of Infection	No. of Patients
Immune deficiency	
Neutropenia	19
Malignant neoplasm/received chemotherapy within 2 wk of presentation	17
Sickle cell disease	2
Urinary tract infection	29
Gastrointestinal tract lesion	
Gastroenteritis	7
Perforated bowel/peritonitis	7
Typhlitis	5
Hepatic failure/ascites	3
Cholangitis	2
Intra-abdominal abscess	1
Necrotizing enterocolitis	1
Bowel obstruction	1
Bacterial meningitis	8
Central venous catheter	5
Pneumonia*	5
Cutaneous lesion	
Cellulitis	2
Abscess	2
Osteomyelitis	1
None identified	6

*Roentgenographic presence of pulmonary infiltrate per pediatric radiologist.

identified. The clinical characteristics of patients with underlying malignant neoplasms and *E coli* bacteremia are given in Table 6.

COMMENT

In our series, the isolation of *E coli* by blood culture was rarely classified as a contaminant, as 90% of instances fulfilled the criteria for clinical sepsis. The frequency of this infection was one per 1000 hospitalized patients and did not exhibit a distinct seasonal distribution. The majority of patients with *E coli* bacteremia were young; two thirds were younger than than 12 months, and one third were younger than 1 month. At the time the original positive blood culture was obtained, patients were febrile in only 64% of cases and required pressor therapy for hypotension in 14% of cases; both rates are lower than those previously documented in a series[3] of children with gram-negative sepsis, in which 91% had fever and 25% had septic shock.

Certain distinctions were noted in the clinical characteristics of children with *E coli* bacteremia related to patient age. Most patients younger than 12 months experienced community-acquired infection (78%) and had no associated immune deficiency identified (91%). By contrast, the majority of patients aged 10 to 18 years had an associated underlying immune deficiency (75%), and nearly one half had nosocomially acquired infection. Very young infants were a distinct subgroup with regard to clinical characteristics and outcome. Compared with those older than 1 month, neonates were significantly more likely to present without fever; specifically, four of six neonates with *E coli* meningitis had an afebrile presentation. *Escherichia coli* sepsis could be a particularly fulminant process in neonates, as evidenced by the fact that these patients accounted for over one half of all instances of hypotension requiring pressor therapy.

Table 6.—Clinical Characteristics of 17 Children With Malignant Neoplasms and *Escherichia coli* Bacteremia

Characteristic	No. (%)
Received chemotherapy within 2 wk of presentation	**17 (100)**
Neutropenia	15 (88)
Aged 10-18 y	13 (76)
Fever	13 (76)
Ampicillin-resistant isolate	10 (60)
Identified portal of infection	8 (47)
Nosocomially acquired infection	6 (35)
Death	5 (29)
Persistent bacteremia	4 (24)
Antibiotic therapy being received when positive blood culture obtained	3 (17)
Hypotension requiring pressor therapy	2 (11)
Polymicrobial bacteremia	1 (6)

Escherichia coli bacteremia was nosocomially acquired in 29% of cases, much lower than the 76% rate of nosocomially acquired pediatric *E coli* bacteremia described by DuPont and Spink.[3] Underlying medical conditions or foci of infection were identified in 90% of cases of pediatric *E coli* bacteremia at the time the original positive blood culture was obtained, which is greater than the 60% rate previously reported.[3] The most frequent were immune deficiencies, urinary tract infections, and lesions of the gastrointestinal tract. In accord with this trend were the findings by DuPont and Spink[3] that underlying malignant neoplasm (with administration of immunosuppressive agents) was the most common chronic disorder associated with pediatric gram-negative sepsis and that the two most commonly identified portals of infection associated with pediatric *E coli* sepsis were the genitourinary and gastrointestinal tracts. A previous series of another cause of pediatric gram-negative bacteremia (*K pneumoniae*[8]) showed a common association with both underlying gastrointestinal tract lesions and immune deficiencies; yet, by comparison with *E coli* bacteremia, sepsis due to this other pathogen was rarely associated (5%) with urinary tract infection. *Escherichia coli* urosepsis was common in young infants, being documented in one third of all patients aged less than 2 months with *E coli* bacteremia.

Escherichia coli has been shown to be one of the most common causes of bacteremia experienced by patients with underlying malignant neoplasms.[4,9] In our series, this pathogen was especially prevalent in children with hematologic malignant neoplasms who received chemotherapy within 2 weeks of the bacteremic episode. The majority of patients with malignant neoplasms were older (76% were aged 10 to 18 years); although the majority of isolates were ampicillin resistant (60%), only one third of infections were nosocomially acquired, and only 17% of patients had been receiving antibiotic therapy at the time the original positive blood culture was obtained. Compared with a previous series of adults with malignant neoplasms and *E coli* sepsis,[9] we found comparable rates of children with persistent bacteremia (24% vs 25%, respectively), fever (96% vs 76%), and an identified portal of infection (51% vs 47%). By contrast with the same series,[10] we found a higher rate of associated neutropenia (52% vs 88%, respectively) and only one half the rate of hypotension requiring pressor therapy. The mortality in our group with underlying malignant neoplasms and *E coli* sepsis was 29%, which was lower than both the 40% mortality for sepsis (all causes) associated with childhood malignant neoplasms[4] and the 73% mortality for gram-negative sepsis in children with malignant neoplasms receiving immunosuppressive therapy.[3]

Certain clinical features were predictive of the outcome of children with *E coli* bacteremia. Patients who were afebrile when the positive blood culture was obtained were more likely to experience a complicated clinical course; compared with those manifesting fever, they experienced significantly greater rates of both persistent bacteremia despite the administration of antibiotics to which the isolate exhibited in vitro sensitivity and ampicillin-resistant isolates. Afebrile presentation is perhaps an index of inadequate host response to *E coli* bacteremia, in that it was significantly associated with the individual variables of neutropenia and persistent bacteremia. Despite this, we did not find a significant difference in mortality between children with and without fever on presentation, which contrasts with the findings of a previous study of adults with *E coli* bacteremia[10] that also compared like presentations. Finally, polymicrobial bacteremia in which *E coli* was a constituent was rare, occurring in only 5% of cases; the mortality observed in this group was not significantly different from that associated with monomicrobial *E coli* bacteremia (although the sample examined was small).

The overall mortality associated with pediatric *E coli* bacteremia was 12%, which is much lower than the 60% mortality reported by DuPont and Spink.[3] The three independent clinical characteristics significantly associated with death were hypotension requiring pressor therapy, presence of a central venous catheter, and neutropenia at the time the original positive blood culture was obtained. A significantly greater mortality was demonstrated in adults with *E coli* sepsis who experienced shock,[3,10] yet the significantly greater mortality in neutropenic than nonneutropenic children with *E coli* bacteremia contrasts with the findings of two previous series of adults with *E coli* bacteremia.[3,10]

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Enrique Freud, MD; Ron Bilik, MD, MS; Isaac Yaniv, MD;
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Factors Associated With Umbilical Catheter-Related Sepsis in Neonates

Susan Landers, MD; Alicia A. Moise, MD; J. Kennard Fraley, MPH; E. O'Brian Smith, PhD; Carol J. Baker, MD

• To determine factors associated with risk for umbilical catheter-related sepsis, we studied neonates with one or more catheters in place for more than 3 days. Among 225 infants with 357 umbilical catheters, catheter-related sepsis occurred in 14 infants (6%). Catheter-related sepsis occurred in 5% of infants with umbilical arterial catheters and in 3% of infants with umbilical venous catheters. Staphylococcal species accounted for 71% of cases of catheter-related sepsis. Multiple logistic regression analysis revealed that very low birth weight and longer duration of antibiotic therapy were significantly associated with risk for umbilical arterial catheter-related sepsis. Increased risk for umbilical venous catheter-related sepsis was best predicted by the simultaneous occurrence of higher birth weight and infusion of hyperalimentation solution. Catheter duration correlated with duration of antibiotic therapy and with infusion of hyperalimentation solution for both types of catheters; however, in the multivariable analysis, duration of catheterization was not found to be a significant independent predictor of risk for catheter-related sepsis for either type of catheter.

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Umbilical arterial catheters (UACs) and umbilical venous catheters (UVCs) provide convenient access to sick neonates. However, these catheters are associated with serious infectious complications, such as nosocomial bacteremia or sepsis. The prevalence of umbilical catheter–related sepsis (CRS) among newborns varies from 3% to 16%.[1-4] Umbilical catheter colonization rates have been reported to be as high as 60%.[4-6]

Because little is known about the factors influencing CRS associated with umbilical catheters, especially in the extremely preterm infant, we sought to determine these risk factors in our neonatal intensive care unit (NICU). We evaluated numerous clinical variables in an effort to identify predictors of CRS and potentially to establish methods for the prevention of CRS in neonates.

SUBJECTS AND METHODS

Subjects

All neonates admitted to the NICU from March 1, 1984, to March 31, 1985, who required umbilical artery and/or venous catheterization for more than 72 hours were studied. Physicians caring for the infants determined the need for catheterization. Most UACs were inserted for blood gas monitoring in neonates with respiratory distress or premature neonates. Most UVCs were placed for administration of fluids and medications to very-low-birth-weight (VLBW) infants (ie, those weighing <1500 g at birth).

Catheter Insertion and Maintenance

Physicians working in the NICU used uniform technique for catheter insertion and maintenance and routinely obtained catheter surveillance cultures, as recommended by the hospital infection control committee.

The umbilicus was disinfected with povidone-iodine solution, excess solution was removed from the skin, and each catheter was inserted with use of sterile technique and secured with sterile suture and tape. Polyvinyl chloride catheters (Argyle Umbilical Vessel Catheter, Sherwood Medical, St Louis, Mo) were used exclusively. The UACs were placed with the tip at the third or fourth lumbar vertebral interspace, and the UVCs were placed in the inferior vena cava at the level of the diaphragm or in the umbilical vein below the liver. Catheter position was confirmed roentgenographically, and improperly positioned catheters were repositioned. The umbilicus remained uncovered, and povidone-iodine solution was applied every 4 hours. All catheter infusates and connecting tubes were changed daily.

Antimicrobial prophylaxis was not given for catheterization. Instead, antibiotics were administered when infection was suspected clinically. Antibiotic therapy included ampicillin and gentamicin for infections acquired before 3 days of life and vancomycin and amikacin with or without ampicillin, ticarcillin, or clindamycin for infections of later onset.

Catheters were infused with 5% or 10% dextrose solution, normal saline solution, or hyperalimentation solution. Each solution contained 1 U of heparin sodium per milliliter. Central strength hyperalimentation fluid contained 20% dextrose, and peripheral strength hyperalimentation fluid contained 12.5% or less. All catheters were infused continuously, except when flushed with heparinized saline after withdrawal of blood samples. Entries into all umbilical catheters were kept at a minimum; however, catheters were used for blood sampling and administration of medications (eg, antibiotics, sodium bicarbonate, and calcium gluceptate) and blood products.

Catheters remaining in place for longer than 7 days were maintained predominantly for infusion of hyperalimentation solutions. Only peripheral strength solutions were infused through UACs. Umbilical venous catheters infusing central strength hyperalimentation solution into the right atrium were entered only for daily solution changes.

Catheter Surveillance Cultures

Weekly surveillance blood cultures were obtained from infants whose catheters were maintained for longer than 7 days. The stopcock was disinfected with povidone-iodine solution, and

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From the Department of Pediatrics, Baylor College of Medicine and Jefferson Davis Hospital, Houston, Tex.

Reprint requests to the Department of Pediatrics, Baylor College of Medicine, One Baylor Plaza, Houston, TX 77030 (Dr Landers).

Table 1.—Cross-Tabulation of Catheter Status and Culture Data*

	Infants With UAC				
	• UAC Cultured	• UAC Not Cultured	No UAC	Total No. of Infants Cultured	Total No. of Infants
Infants with UVC					
• UVC cultured	108†‡	24†	12	144	179
• UVC not cultured	35‡	. . .	. . .	. . .	
No UVC	46	. . .	. . .	. . .	
Total No. of Infants Cultured	189	. . .	. . .	. . .	. . .
Total No. of infants	213			. . .	225

*UAC indicates umbilical arterial catheter; UVC, umbilical venous catheter.

†Infants with UVC cultured and a simultaneous UAC: 108+24=132.

‡Infants with UAC cultured and a simultaneous UVC: 108+35=143. Infants with both a UAC and UVC: 108+24+35=167.

1 mL of blood was withdrawn through the catheter and placed in thioglycollate broth. When any surveillance catheter culture was positive, a blood culture was obtained from a peripheral vessel within 24 to 48 hours. The catheter was maintained only if the infant remained asymptomatic and the subsequent peripheral blood culture was sterile. Catheters were maintained in infants treated for early-onset sepsis (sepsis occurring during the first 3 days of life) who had negative blood cultures following therapy and in whom the catheter was necessary for care.

Catheters were removed when (1) an infant with a positive surveillance culture either manifested clinical signs of sepsis or had a confirmatory positive peripheral blood culture, (2) the catheter was no longer needed for care, or (3) a noninfectious complication of catheterization occurred. When a catheter was removed, the tip was cut off with sterile scissors and placed in thioglycollate broth. All surveillance cultures were processed by standard bacteriologic methods for identification of isolates and their antimicrobial susceptibility.

Definitions

A "culture-negative" infant was one in whom all surveillance blood and catheter tip cultures were sterile and who remained asymptomatic. A "colonized infant" was an infant with a positive surveillance catheter blood culture or catheter tip culture, who also had a sterile peripheral blood culture and who was not clinically ill.[7,8] An infant was diagnosed as having CRS when the infant was clinically ill with no other obvious source for bacteremia and had either a positive blood culture obtained through the catheter and a peripheral blood culture positive for the same organism[7,9,10] or had cultures of the catheter tip and the peripheral blood positive for the same organism.[8,11]

Clinical Variables

We recorded birth weight, number and duration of catheterization(s), simultaneous UAC and UVC placement, predominant catheter infusate, type and duration of antimicrobial therapy, and all noninfectious complications for each infant. For infants with multiple catheters, the sum of days duration for each catheter was considered the total duration of catheterization. If more than one infusate was used, the solution that was infused for the longest time was analyzed. Only antibiotics administered before final catheter removal or before onset of documented CRS were analyzed. Noninfectious, thrombotic, or vasospastic catheter-related events consisted of any occurrence of dampened blood pressure wave form, clotted catheter, pale or cyanotic "catheter toes," decreased pulses, or altered perfusion distal to the cathet for which a catheter was removed or replaced.

Statistical Methods

All data are expressed as mean and SD or as percentages an their 95% confidence intervals (CIs). Potential factors associate with CRS were analyzed for UACs and UVCs separately. Ca egorical variables were analyzed by χ^2, and continuous variabl were analyzed by *t* test.

To determine the independent contribution of each variabl and which variable(s) best predicted CRS, multiple logistic r gression analysis was performed. The multivariable analysis ac justed for possible correlations between variables and served t overcome the inflation in type I error associated with repeate univariate significance testing. The occurence of CRS was th dependent variable and was regressed on all other independer variables. The data from infants with UACs were analyzed sep arately from data from infants with UVCs. Simultaneous UA and UVC catheterization was included as one of the variables so that for each infant the presence of both types of catheters wa analyzed as a confounding variable.

RESULTS

Frequency of CRS and Demographic Data

Two hundred twenty-five infants had one or more cath eters in place for longer than 72 hours. Their mean birt weight was 1560 g (SD, 865 g), with a range of 620 to 470 g. Twenty-three percent weighed less than 1000 g, 50% weighed 1001 to 1500 g, 9% weighed 1501 to 2000 g, an 18% weighed more than 2001 g. Their mean gestationa age was 31.3 weeks (SD, 4.1 weeks).

Fourteen infants developed CRS (14/225 [6%]). Ten ha CRS associated with a UAC and four had CRS associate with a UVC. Thirty-nine percent of infants (87/225) wer colonized, and 55% (124/225) had sterile surveillance cultures.

Overall, the infants had 1.6 (SD, 0.8) catheters each, with a range of one to six catheters. Twenty percent (46/225) of infants had a UAC only, 75% (167/225) had both a UAC and a UVC, and 5% (12/225) had a UVC only. Culture data were available for analysis from 189 of the 213 infants with UACs and from 144 of the 179 infants with UVCs. Table 1 presents a cross-tabulation of the infants' catheter status and available catheter culture data. To describe the prevalence of CRS and to determine risk factors for CRS, the multivariable analysis examined only data from those infants with catheters and available culture data. The multivariable analysis examined data from infants (cultured) for each catheter type separately (UAC and UVC) and accounted for simultaneous UAC and UVC catheterization as a confounding variable within the analysis. Repeated analysis of the same infants did not occur, except for those infants who had simultaneous UAC and UVC catheterization and culture data available for each catheter type. At the time of diagnosis of CRS, exact catheter status was known for each of the 10 infants with UAC-related CRS and each of the four infants with UVC-related CRS, and their catheter status did not change during either analysis.

The prevalence of CRS among infants with UACs was 5% (10/189) and among those with UVCs was 3% (4/144). Catheter colonization was noted more often among infants with UACs (76/189 [40%]) than UVCs (32/144 [22%]) ($P<.002$). Colonization of either catheter type occurred more often among infants who weighed more than 1500 g at birth (31/61 [51%]) than among VLBW neonates (56/164 [34%]) ($P<.03$).

Simultaneous UAC and UVC catheterization was common. Seventy-five percent of infants had both a UAC and a UVC in place at some time. However, the majority of

Table 2.—Variables Assessed as Potential Risk Factors for UAC-Related CRS*

Risk Factor	UAC-Related CRS	No CRS	Univariate Significance	Multivariate Significance
Catheter duration, d	16.9 (8.9)	10.7 (7.0)	$P = .059$	NS
Birth weight, g [range]	959 (221) [620-1270]	1609 (874) [660-4700]	$P < .001$	$P < .02$
VLBW infants	10/10 (100)	127/179 (71)	. . .	. . .
Antibiotic therapy, d	9.7 (4.5)	5.0 (3.6)	$P < .01$	$P < .02$
Antibiotics at catheter removal	7/10 (70) [34-94]	40/179 (22) [16-29]	$P < .001$	$P < .02$
Hyperalimentation infusate	7/10 (70) [34-94]	47/179 (26) [19-33]	$P < .01$	NS
Vascular complication	6/10 (60) [25-88]	44/179 (25) [19-32]	$P < .05$	NS
Total No. of catheters per infant	2.5 (1.1)	2.1 (0.8)	NS	NS
Simultaneous UAC and UVC catheterization	8/10 (80) [42-98]	135/179 (75) [68-82]	NS	NS

*UAC indicates umbilical arterial catheter; CRS, catheter-related sepsis; VLBW, very-low-birth-weight; NS, not significant ($P > .05$); and UVC, umbilical venous catheter. Data are mean (SD) or number/total number (percent); values in brackets are 95% confidence interval, unless otherwise stated.

†Univariate analysis by *t* test for continuous variables, and χ^2 test for categorical variables.

infants who developed CRS had only one type of catheter in place when CRS was diagnosed; the other catheter had been removed days previously. Among the 10 infants with UAC-related CRS, two had a UAC alone and eight had both a UAC and a UVC at some time. Six of these eight infants with UAC-related CRS had a UVC simultaneously, but had both catheters cultured so that it was possible to ascertain which catheter had caused the CRS, or their UVC had been removed days earlier with negative surveillance cultures at that time. In the other two infants with UAC-related CRS, the UVC had been removed more than 4 days previously, although it was not cultured. Similarly, among the four infants with UVC-related CRS, one infant had a UVC alone; the other three infants had both UAC and UVC cultured at the time of diagnosis of UVC-related CRS (two of the three) or their UAC had been removed days earlier. So, for each case of CRS, despite simultaneous UAC and UVC catheterization, adequate culture data were available or the other catheter had been removed days previously, permitting accurate assessment of catheter status and diagnosis of CRS.

Sixty-five percent of catheters were removed electively (the catheter was no longer needed for care). Twenty-two percent were removed because of a noninfectious, vascular complication. Thirteen percent fell out accidentally or were removed for other reasons, such as necrotizing enterocolitis. Culture-proven early-onset sepsis was not an indication for catheter removal.

Causative Agents

Staphylococci were the most common isolates from infants with colonized catheters (80%) and from those who developed CRS (10/14 [71%]). Coagulase-negative staphylococci were the most frequent cause of CRS (6/14 [43%]). *Staphylococcus aureus* (4/14 [28%]) and gram-negative bacilli (3/14 [21%]) accounted for the majority of the other cases of CRS. One case of CRS was due to *Candida* species. During the period of study, 67% of coagulase-negative staphylococcal isolates from all neonatal blood and cerebrospinal fluid cultures were resistant to methicillin, while 100% of isolates causing CRS were methicillin resistant ($P < .02$).

Surveillance Cultures

Eighty-two surveillance blood cultures were drawn through catheters remaining in place for longer than 7 days. Sixteen cultures were positive, six of which accurately identified CRS. The sensitivity and specificity of this surveillance method were 67% (95% CI, 30% to 92%) and 86% (95% CI, 75% to 94%), respectively. The positive predictive value calculated for catheter blood cultures was 37% (95% CI, 14% to 65%).[12]

There were 121 positive catheter tip cultures among the 351 tip cultures obtained. Only 12 of the positive tip cultures accurately identified CRS. For the diagnosis of CRS, this method of surveillance had a sensitivity of 92% (95% CI, 63% to 99%) and a specificity of 68% (95% CI, 63% to 72%). A very low positive predictive value of 10% (95% CI, 5% to 17%) was found for catheter tip cultures.[12]

Analysis of Risk Factors for UAC-Related CRS

Table 2 summarizes the factors evaluated by both univariate and multiple logistic regression analyses. The multivariable analysis revealed that VLBW was the best predictor of risk for CRS in infants with UACs ($P < .02$). Duration of antibiotic therapy and antibiotic therapy at catheter removal were also significant, although interchangeable, in their ability to predict risk for CRS ($P < .02$). The odds of an infant developing CRS if he or she had received antibiotics at the time of UAC removal were 6.2 times that if he or she had not. The odds of developing CRS were 1.2 times greater for each day of antibiotic administration.

Prolonged UAC catheterization was not found to be significant as an independent risk factor for CRS after birth weight and antibiotic therapy were introduced into the multivariable analysis. Duration of UAC correlated with both duration of antibiotic therapy ($r = .651$, $P < .001$) and with use of hyperalimentation solution ($r = .616$). Similarly, infusion of hyperalimentation solution through a UAC was not significant as an independent risk factor for CRS after adjusting for other variables. Although birth weight correlated inversely with the total number of catheters ($r = -.264$, $P < .001$), neither simultaneous UVC catheterization nor multiple UAC catheterizations was significant as an independent risk factor for CRS in the multivariable analysis.

Table 3 summarizes the relationship between several of the independent variables that were correlated. Umbilical arterial catheters infused with hyperalimentation fluid

Table 3.—Relationships Between Selected Risk Factors*

	Hyperalimentation Solution	No Hyperalimentation Solution	Univariate Significance†
Variables for UAC-related CRS			
Birth weight, g	1206 (654)	1722 (895)	$P<.001$
Antibiotic duration, d	7.4 (4.5)	4.4 (3.1)	$P<.001$
Catheter duration, d	18.0 (7.6)	8.2 (4.7)	$P<.001$
Variables for UVC-related CRS			
Birth weight, g	1858 (1248)	1262 (513)	$P<.02$
Antibiotic duration, d	6.6 (4.9)	4.3 (2.2)	$P<.02$
Catheter duration, d	12.5 (5.4)	6.8 (2.1)	$P<.001$

*Data are mean (SD). UAC indicates umbilical arterial catheters; CRS, catheter-related sepsis; and UVC, umbilical venous catheters.
†Univariate analysis by two-sample *t* test.

were maintained longer than those that infused other solutions. In addition, smaller infants tended to have hyperalimentation fluid infused through their UACs. These correlations probably explain why UAC infusion with hyperalimentation fluid was associated significantly with CRS in the univariate but not in the multivariable analysis.

Because duration of antibiotic therapy was a significant predictor of risk for UAC-related CRS, we examined why infants with UACs received prolonged antibiotic therapy. Among infants with UACs, 12% (23/189) received antibiotic therapy for more than 10 days. Culture-proven early-onset sepsis was the indication in 26% (6/23) of cases. Clinical suspicion of sepsis (without positive cultures) or nosocomial pneumonia were indications in 74% (17/23) of cases.

Analysis of Risk Factors for UVC-Related CRS

Factors evaluated by both univariate analysis and multiple logistic regression analysis are summarized in Table 4. The multivariable analysis revealed that overall risk of UVC-related CRS was greatest for infants with higher birth weight ($P<.05$). In addition, the presence of two factors interacting—birth weight and infusion of hyperalimentation solution—was significant as a predictor of risk for UVC-related CRS ($P<.05$).

Duration of UVC catheterization was not a significant independent predictor of risk for CRS after antibiotic therapy and hyperalimentation fluid were accounted for in the multivariable analysis. Risk for UVC-related CRS was not influenced significantly by duration of antibiotic therapy, multiple or simultaneous catheterizations, or the occurrence of vascular complications.

Table 3 illustrates that UVC infusion with hyperalimentation fluid correlated with birth weight and with catheter duration ($r=.321$ and $r=.607$ [$P<.001$], respectively). Larger infants tended to have UVCs infused with hyperalimentation fluid. Infants with hyperalimentation fluid infusing through their UVCs were catheterized longer than those who had other solutions infused.

COMMENT

Few data are available concerning CRS or bacteremia associated with umbilical catheters,[1-5] especially for VLBW neonates who require catheters for more than a few days. In our study, CRS occurred in 6% of infants who required catheterization for more than 3 days. As expected, the majority of these were VLBW infants. Utilizing a similar definition of CRS, Bard et al[2] reported a frequency of 3%, but most of the 75 infants in their study had catheters in place for less than 4 days and weighed more than 1500 g. In our study, infants tended to develop CRS from UACs slightly more frequently (5%) than from UVCs (3%), but this difference was not statistically significant. Similarly, Hall and Rhodes[3] analyzed CRS by umbilical vessel site and found a frequency of UAC-related CRS of 16% and a frequency of UVC-related CRS of 11%.

As with catheter-related infections in older patients, the most common causative agents for umbilical CRS in neonates were staphylococci. Coagulase-negative staphylococci were the most frequent isolates, and all were resistant to methicillin but susceptible to vancomycin. Coagulase-negative staphylococci frequently cause nosocomial sepsis in VLBW neonates, and most strains are resistant to methicillin.[9,13,14] In adults with central venous catheters, *Staphylococcus epidermidis* is the most frequent organism colonizing catheters and causing CRS.[8,15] The virulence properties of certain strains, their antibiotic resistance patterns, and the immature immunologic status of neonates all account for their prevalence in causing CRS.[9,16] Properties of the umbilical catheter itself may be influential, as slime-producing coagulase-negative staphylococci preferentially adhere to surface irregularities of the polyvinyl chloride catheter and account for a majority of CRS isolates.[17,18] Other cases of CRS in our study were due to *S aureus*, gram-negative bacilli, and *Candida* species, agents commonly causing CRS in adults.[8]

A major finding in our study was that risk for CRS from UACs was related to both VLBW and longer duration of antibiotic therapy. Other reports have documented the higher risk for nosocomial sepsis among VLBW infants.[14,19,20] However, the influence of prolonged antibiotic therapy on the risk for CRS has not been described, to our knowledge. Prolonged antibiotic therapy may increase the risk for CRS by increasing the prevalence of resistant organisms, or it may be a marker for overall severity of illness and susceptibility to infection. Bard et al[2] noted that prophylactic antibiotics given for umbilical catheterization decreased catheter colonization but did not prevent CRS. In our study, prolonged administration of broad-spectrum antibiotic therapy was associated with increased risk for CRS predominantly among VLBW infants treated for multiple episodes of presumed sepsis or nosocomial pneumonia.

For infants with UVCs, the occurrence of two factors interacting—higher birth weight and infusion of hyperalimentation fluid—influenced risk for CRS. This is in agreement with the report of Munson et al[13] that UVCs and central venous catheters infusing hyperalimentation fluid often led to coagulase-negative staphylococcal sepsis in neonates. Every infant in our study who developed UVC-related CRS had central strength hyperalimentation

Table 4.—Variables Assessed as Potential Risk Factors for UVC-Related CRS*

Risk Factor	UVC-Related CRS	No CRS	Univariate Significance†	Multivariate Significance
Catheter duration, d	11.8 (3.6)	8.1 (3.9)	NS	NS
Birth weight, g [range]	3530 (1195) [1860-4700]	1342 (691) [620-4050]	$P<.05$	$P<.05$‡
VLBW infants	0/4 (0)	123/140 (88)	. . .	. . .
Antibiotic therapy, d	4.0 (6.2)	4.9 (3.1)	NS	NS
Antibiotics at catheter removal	1/4 (25) [0-100]	49/140 (35) [27-43]	NS	NS
Hyperalimentation infusate	4/4 (100) [0-100]	30/140 (21) [14-28]	$P<.001$	$P<.05$‡
Vascular complication	2/4 (50) [0-100]	6/140 (4) [0-7]	$P<.0001$	NS
Total No. of catheters per infants	2.3 (0.5)	2.2 (0.7)	NS	NS
Simultaneous UAC and UVC catheterization	3/4 (75) [0-100]	129/140 (92) [87-97]	NS	NS

*UAC indicates umbilical arterial catheter; CRS, catheter-related sepsis; VLBW, very-low-birth-weight; NS, not significant ($P>.05$); and UVC, umbilical venous catheter. Data are mean (SD) or number/total number (percent); values in brackets are 95% confidence intervals, unless otherwise stated.

†Univariate analysis by *t* test for continuous variables and χ^2 test for categorical variables.

‡Value represents significance for interaction of birth weight and hyperalimentation fluid.

fluid infusing the catheter. In contrast, the infusion of peripheral strength hyperalimentation fluid through UACs was not a significant risk factor for UAC-related CRS.

We anticipated that longer duration of catheterization would predict risk for CRS. Band and Maki[11] found that both catheter colonization and CRS were related to duration of arterial catheterization, presumably because multiple entries into a catheter increase the risk of infection over time. Similarly, Adam et al[21] reported that longer catheter duration was associated with positive cultures of umbilical catheters. In our study, prolonged catheterization was not an independent risk factor for CRS, most likely because of the correlations that existed between catheter duration, antibiotic therapy, and infusion of hyperalimentation fluid for both catheter types.

Certain variables that we studied (specifically, catheter duration and infusion of hyperalimentation solution) were found to be significant by univariate testing but became insignificant by multivariate testing. This can be explained as a result of interactions and correlations that were found to exist between certain independent variables. This multicollinearity, the finding that some of the predictor variables are highly correlated with each other, is troublesome assessment of the independent significance of prolonged catheterization. When some of the independent variables are highly correlated (such as antibiotic therapy and catheter duration), the multivariable analytic model may retain one variable, such as antibiotic therapy, as a significant risk factor at the cost of diminishing the possible contribution of other variables, such as prolonged catheter duration. If antibiotic therapy had not been introduced into and accounted for in the analysis, then it is possible that prolonged catheter duration might have been a significant independent variable or predictor for CRS.

The best method for detection of catheter colonization has been controversial. Routine cultures of catheter tips at removal may overestimate colonization[21]; as a result, semiquantitative catheter culture techniques have been recommended to enhance specificity.[7,8,10,21] Nevertheless, we performed routine tip cultures and blood cultures obtained through catheters periodically to evaluate each technique's ability to predict CRS. Some catheters determined to be colonized may have been contaminated at the site of blood withdrawal; without semiquantitative cultures or histopathologic examination of catheter tips, our definition of catheter colonization cannot be confirmed.[7] However, our low rate of catheter colonization compared with that previously reported suggests that colonization was not overestimated. The surveillance culture methods correctly predicted CRS in only 10% to 38% of infants subsequently documented to have CRS. However, blood cultures drawn through umbilical catheters may be useful to predict CRS, with the advantage of being performed while the catheter remains in place.

CONCLUSIONS

The benefits from the use of umbilical catheters must be assessed daily and weighed against risk for infection, particularly in VLBW infants. Our results reveal certain factors that significantly influence risk for umbilical CRS. Infusion of hyperalimentation fluid through the UVC places an infant at higher risk for infection. Very low birth weight and prolonged antibiotic therapy increase risk for CRS from UACs. Prolonged catheterization, generally greater than 2 weeks, should be avoided whenever possible.

We do not advocate the widespread use of catheter surveillance cultures. Bloods cultures obtained through catheters, together with peripheral blood cultures, may be of diagnostic benefit in cases where umbilical CRS is clinically suspected.

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A 50-Year Follow-up of Childhood Plumbism

Hypertension, Renal Function, and Hemoglobin Levels Among Survivors

Howard Hu, MD, MPH, ScD

• A group of 192 subjects with well-documented lead poisoning in 1930 to 1942 were identified in this pilot study. Thirty-five of 72 survivors traced to a Boston area address and 22 age-, sex-, race-, and neighborhood-matched controls were recruited into a clinical study. One matched subject with plumbism had grossly abnormal renal function and an elevated blood lead level of an unclear cause. Among the remaining 21 matched pairs, the risk of hypertension was significantly higher in subjects with plumbism (relative risk, 7.0; 95% confidence interval, 1.2 to 42.3). Mean adjusted creatinine clearance rates for subjects with plumbism, however, were significantly higher than those of controls and supranormal in comparison to rates predicted for sex and age. Subjects with plumbism had significantly lower hemoglobin concentrations and hematocrit readings than the controls. Blood lead and serum creatinine levels were low for both groups. These results suggest that survivors of childhood lead poisoning have an increased risk of clinically significant hypertension developing in the setting of supranormal creatinine clearance rates.

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The immediate effects of exposure to high amounts of lead are well known. Intense interest has focused on the long-term effects of lead exposure.[1] Such effects include those caused by continuous exposure to low levels of lead from outside sources as well as the long-term sequelae of lead poisoning.

Pediatric lead exposure continues to be a widespread phenomenon in our society.[2,3] There is growing evidence, moreover, that lead that accumulates in the skeleton is more metabolically active than previously thought[4,5] and may exert multisystemic effects late in life.

Most studies on the long-term effects of pediatric lead exposure have been directed at measuring neuropsychological outcomes. Few have assessed other long-term consequences. High rates of renal disease–associated morbidity and mortality have been reported among adults who had histories of childhood lead poisoning in Queensland, Australia.[6,7] In contrast, investigators in the United States failed to find significant chronic nephropathy among patients studied up to 20 years after childhood lead intoxication.[8-10] To our knowledge, the risk of hypertension without kidney disease or injury to other organ systems has not been closely examined.

In this pilot study, subjects who had well-documented evidence of childhood plumbism in the period 1930 to 1942 were recruited for a detailed investigation of renal, cardiovascular, hematopoietic, and neurobehavioral function. Although small in scale, the investigation had several advantages over previous studies, including the use of strict criteria to define childhood plumbism, the long duration of follow-up, the simultaneous study of a matched control group, and the range of outcomes studied. All research described herein was approved by the Institutional Review Boards of the Brigham and Women's Hospital, Boston Children's Hospital and Medical Center, and the Harvard School of Public Health, Boston, Mass.

SUBJECTS AND METHODS

Defining the Eligible Study Population

The diagnosis of the lead poisoning was based largely on clinical grounds until 1930, when the finding of radiologic evidence of lead's effect was reported in the literature by Vogt[11] of Boston Children's Hospital. This finding is otherwise seen only in patients with rickets, which, in turn, is associated with other characteristic findings (eg, bow deformity of the lower extremities).

This study began with a review of microfilmed medical records of all 322 patients who had been given a diagnosis (primary, secondary, or other) of lead poisoning while at Boston Children's Hospital from 1930 to 1942 and who survived hospitalization. To be eligible for further consideration, a patient needed medical record documentation that fulfilled the following four major criteria based on history, clinical presentation, and radiologic evidence: (1) a definite history of pica for lead-containing material (usually paint) or the use of lead nipple shields; (2) evidence of dense metaphyseal bands ("lead lines") on at least one long bone roentgenogram; (3) clinical evidence of symptoms and signs characteristic of childhood lead intoxication; and (4) the absence of clinical evidence for rickets.

The 192 subjects who remained were divided into three categories based on clinical severity of lead intoxication (Table 1). The classification scheme corresponds to ranges of blood lead concentration that have a small amount of overlap and can serve as approximate indicators of the level of poisoning.[12,13] All subjects for whom race was recorded were white.

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From the Channing Laboratory, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, and the Occupational Health Program, Departments of Environmental Health and Physiology and Epidemiology, Harvard School of Public Health, Boston, Mass.

Reprint requests to Brigham and Women's Hospital, Department of Medicine, Channing Laboratory, 180 Longwood Ave, Boston, MA 02115 (Dr Hu).

Table 1.—Scoring System for Severity of Childhood Plumbism

Score	Symptoms/Signs	Blood Lead Level at Which Symptoms/ Signs Begin, μmol/L
1	Abdominal pain, constipation, vomiting, anorexia, or hyperirritability	2.9-4.8
2	Score 1 symptom(s) plus nerve palsy	4.3-5.8
3	Score 1 symptom(s) plus sign(s) of encephalopathy (somnolence, semistupor, coma, convulsion, or projectile vomiting)	5.8

Tracing of Subjects

Tracing of the 192 eligible subjects was performed using available public records of state and local governments, including birth, marriage, and death certificate records from the state Registry of Vital Records and Statistics, voting lists from state records, drivers license records from the state Registry of Motor Vehicles, and local telephone books. Records of parents and siblings were inspected that provided listings of survivors.

One hundred two eligible subjects were traced to current Massachusetts addresses (Fig 1). Death certificates were obtained on 43 subjects. The 47 remaining subjects (24% of the 192 eligible subjects) were either traced to an out-of-state address or were unavailable for follow-up. As could be expected, dead subjects had a high odds for having had poor Plumbism Severity Scores (2 or 3) in comparison with either all the other eligible subjects (odds ratio [OR], 2.21; 95% confidence interval [CI], 1.04 to 4.67) or survivors who were traced to current Massachusetts addresses (OR, 2.79; 95% CI, 2.14 to 6.30).

Recruitment of Subjects

Of the 102 subjects traced to current Massachusetts addresses, a subgroup of 72 who lived within a 48-km radius of the Ambulatory Clinical Research Center in Boston were targeted for recruitment. Each subject was sent a letter that specifically described the project as a scientific study on "the impact of the environment on health," in which the addressee had been identified as someone who had been "exposed to lead and admitted to Children's Hospital." The evaluation was explained as consisting of a questionnaire, interview, and "simple tests of kidney and neurologic function." Subjects were offered $50 to $75 as compensation for participation, the amount depended on the distance necessary for the subject to travel to participate. Letters were followed by telephone calls to subjects who had not responded.

Thirty-five subjects agreed to participate in the study and followed through on their visit. Fifteen expressed interest in the study but could not schedule a visit to the Ambulatory Clinical Research Center. Seven refused outright to participate in the study. Fourteen did not live at the address listed or did not respond to letters or telephone calls. One subject was found to have died several months prior to the study. Study participants had a low odds (but not statistically significant) of having a Severity Score of 2 or 3 in comparison with all the other nondead subjects (OR, 0.50; 95% CI, 0.18 to 1.34) and the nonparticipating subjects who had been traced to Massachusetts (OR, 0.63; 95% CI, 0.21 to 1.85) or Boston-area addresses (OR, 0.52; 95% CI, 0.15 to 1.72).

Recruitment of Control Subjects

Potential control subjects matched on age (within 2 years), sex, race, and neighborhood (voting precinct) were identified using information derived from town books. Within 4 weeks of evaluating the index case, letters of recruitment were mailed to two potential controls, followed by telephone calls using numbers from telephone book listings. The letter of recruitment specifically described the project as an "approved scientific study on the impact of the environment on health" in which we were focusing on "kidney and nerve function." Subjects were offered $50 to $75 as compensation for participation, the amount depending on the distance necessary for the subject to travel to participate. Failure to respond within 2 weeks or refusal led to successive cycles of recruitment mailing and calling to other potential controls. Subjects were excluded if they had a history of lead intoxication as a child (none did).

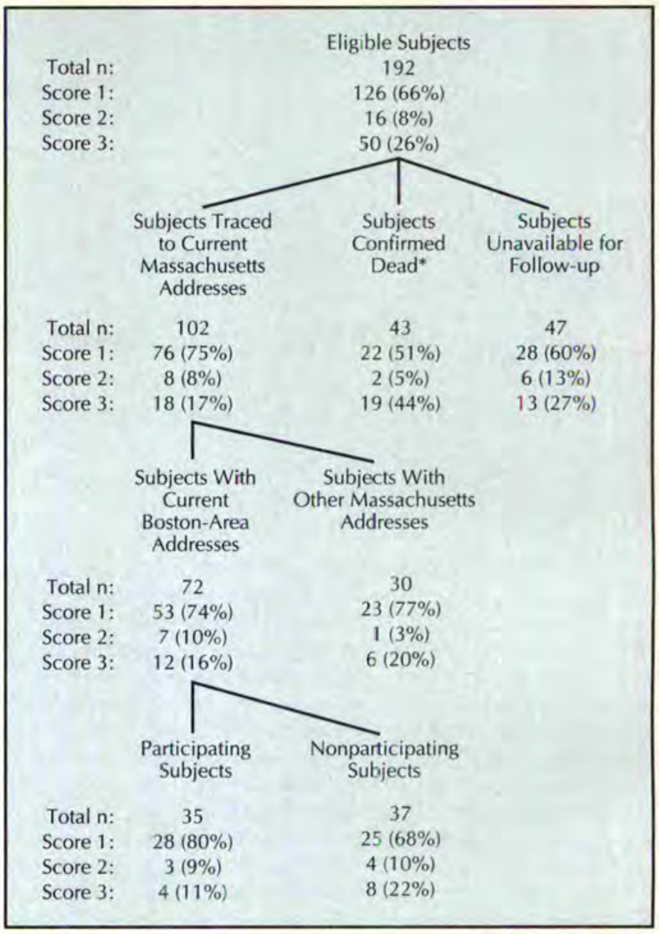
Eligible Subjects
Total n: 192
Score 1: 126 (66%)
Score 2: 16 (8%)
Score 3: 50 (26%)
Subjects Traced to Current Massachusetts Addresses
Subjects Confirmed Dead*
Subjects Unavailable for Follow-up
Total n: 102 43 47
Score 1: 76 (75%) 22 (51%) 28 (60%)
Score 2: 8 (8%) 2 (5%) 6 (13%)
Score 3: 18 (17%) 19 (44%) 13 (27%)
Subjects With Current Boston-Area Addresses
Subjects With Other Massachusetts Addresses
Total n: 72 30
Score 1: 53 (74%) 23 (77%)
Score 2: 7 (10%) 1 (3%)
Score 3: 12 (16%) 6 (20%)
Participating Subjects
Nonparticipating Subjects
Total n: 35 37
Score 1: 28 (80%) 25 (68%)
Score 2: 3 (9%) 4 (10%)
Score 3: 4 (11%) 8 (22%)

Fig 1.—*Breakdown on tracing, recruitment, and plumbism severity scores. Score 1 indicates abdominal pain, constipation, vomiting, anorexia, or hyperirritability; score 2, score 1 symptom(s) plus nerve palsy; score 3, score 1 symptom(s) plus sign(s) of encephalopathy; and asterisk, death certificate obtained.*

Twenty-two control subjects were recruited in this fashion. Seven were recruited in the first mailing; eight were recruited in the second mailing; one was recruited in the third mailing; four were recruited in the fourth mailing; and two were recruited in the fifth mailing. Exhaustion of the pilot study's funding curtailed further recruitment, and 13 subjects with childhood plumbism were left without matched controls. Unmatched subjects with plumbism tended to live farther away from Boston than the matched subjects with plumbism, which may partially explain the difficulty in recruiting more controls after five mailings.

Evaluation Protocol

Each participant received a package containing a self-administered questionnaire and instructions. The questionnaire elicited information on childhood hospitalizations and illnesses, occupations, hobbies, potentially hazardous exposures, smoking, alcohol ingestion and other drug use, adult hospitalizations, reproductive histories, medications, and chronic diseases (ie, high blood pressure, diabetes, gout, and kidney disease). A subject was classified as receiving antihypertensive medications if taking daily doses of any medication listed by the American Hospital Formulary Service as a hypotensive or diuretic agent, or any β-blocker or calcium channel–blocking agent.

During the visit to the Ambulatory Clinical Research Center, each subject underwent a 3-hour timed urine collection, brief physical examination, a 1½ -hour battery of neuropsychological

Table 2.—Participant Demographics and Severity Scores

	Matched Subjects With Plumbism	Matched Control Subjects	Unmatched Subjects With Plumbism
n	22	22	13
Age, y			
Range	49-60	48-60	47-60
Mean (SD)	54.7+4.0	55.4+4.0	56.7+4.0
Sex M/F	8/14		5/8
Plumbism Severity Score, No.(%)			
1	19 (86)	. . .	9 (69)
2 or 3	3 (14)	. . .	4 (31)
Education, y			
Range	8 -20	8-18	11-18
Mean (SD)	13.5+2.8	14.3+2.9	12.9+1.9
Smoking			
Never	8	7	5
Former	11	12	5
Current	3	3	3
Alcohol Ingestion			
<2 alcoholic drinks per day	19	20	12
⩾2 alcoholic drinks per day	3	2	1
Body Mass Index kg/m²			
Range	21.5-38.3	20.1-40.0	22.4-37.5
Mean (SD)	28.4+5.5	27.7+5.1	28.8+4.6

tests, and phlebotomy. Systolic blood pressure and fifth-phase diastolic blood pressure were measured to the nearest 2 mm Hg, which were taken from the right and left arms while the subject was in the sitting position by a research nurse who was unaware of the subject's classification as lead-exposed or control. A subject's blood pressure was considered elevated if, based on the average of readings from the right and left arm, the systolic blood pressure was greater than 140 mm Hg or the diastolic blood pressure was greater than 90 mm Hg. All subjects with childhood plumbism and their matched controls were given the same evaluation protocol.

Laboratory Tests

The 3-hour timed urine collections underwent standard urinalysis with measurement of creatinine level. Urinary creatinine values were compared with serum creatinine values; creatinine clearance rates were calculated adjusted to a body surface area of 1.73 m². Blood specimens were assayed for standard serum chemistry studies, serum urea nitrogen, and creatinine by standard multichannel computerized analysis (Technicon SMAC-2, Technicon, Tarrytown, NY). Complete blood cell counts were performed by an automated cell counter (Coulter, STK-R, Coulter Corp, Hialeah, Fla). Blood specimens that had been collected in metal-free heparinized tubes were assayed for blood lead level using graphite atomic absorption spectroscopy and zinc protoporphyrin level by hematofluorometry (ESA Labs, Bedford, Mass).

Statistical Analyses

Continuous variable data for matched pairs of plumbism and control subjects were plotted; means were compared using paired *t* tests. For each subject, creatinine clearance rate also was compared with the age- and sex-specific expected value generated by the nomogram developed by Rowe et al.[14] Discrete outcomes were compared by analyzing discordant pairs using McNemar's test and calculating relative risks and 95% CIs.[15]

RESULTS

Demographics, Mortality, and Reproductive and Neurobehavioral Outcomes

Table 3.—Comparison of Selected Laboratory Values

Factor	Subjects Matched With Plumbism	Matched Control Subjects	*P* Value*	Unmatched Subjects With Plumbism
Blood lead, µmol/L				
Range	0.9-0.53	0.19-0.87		0.19-0.48
Mean (SD)	0.29 (0.11)	0.36 (0.19)	.23	0.30 (0.11)
Zinc protoporphyrin, µg/dL				
Range	6-84	15-79		19-72
Mean (SD)	36.4 (22.8)	32.2 (16.8)	.55	29.8 (16.2)
Serum creatinine, µmol/L				
Range	50-130	60-100		60-130
Mean (SD)	90 (20)	90 (20)	.77	90 (10)
Serum urea nitrogen, mmol/L				
Range	3.6-24.6	3.2-8.6		3.2-16
Mean (SD)	5.9 (1.5)	5.7 (1.1)	.61	6.7 (3.4)
Creatine clearance rate, mL/s per 1.73 m²				
Range	1.08-2.62	0.78-2.33		0.88-2.97
Mean (SD)	1.88 (0.33)	1.48 (0.48)	.00	1.68 (0.50)
Serum uric acid, µmol/L				
Range	190-460	180-430		170-600
Mean (SD)	330 (80)	320 (70)	.45	360 (120)
Hemoglobin, g/L				
Range	120-152	128-171		122-169
Mean (SD)	138 (11)	147 (12)	.01	145 (15)
Hematocrit				
Range	0.35-0.45	0.39-0.5		0.37-0.5
Mean (SD)	0.41 (0.03)	0.43 (0.32)	.02	0.43 (0.04)
Mean cell volume				
Range	81-99	82-95		80-92
Mean (SD)	86.0(12.9)	86.3(17.8)	.95	84.0(12.8)

*Comparing matched subjects with plumbism with control subjects.

Matched subjects with plumbism, matched controls, and nonmatched subjects with plumbism were similar with respect to age, sex ratio, body mass index, years of education, alcohol ingestion, and smoking status (Table 2). A higher proportion of nonmatched subjects with plumbism had high severity scores. All subjects were white.

Hypertension

Among the 22 matched pairs of subjects with plumbism and controls, three (14%) of the controls reported taking daily medications that were classified as antihypertensive, as opposed to nine (41%) of the subjects with plumbism. Each of these controls took a single agent, with two taking β-blockers and one taking a diuretic. Among subjects with plumbism, five were receiving single agents, with two receiving β-blockers, two receiving angiotensin-enzyme inhibitors, and one receiving a diuretic. Three subjects with plumbism were taking two agents, and one was taking a combination of three. There were seven discordant pairs in which the subject with plumbism was taking antihypertensive medications but the control subject was not, compared with one discordant pair in which the subject with plumbism was not taking medications but the control subject was (relative risk, 7.0; 95% CI, 1.2 to 42.3). Of the matched study participants not taking antihypertensive medications, an additional five subjects with plumbism and five controls had elevated blood pressure on physical examination. The ratio of discordant pairs for subjects either taking antihypertensive medications or having elevated blood pressures was also 7:1. Mean systolic blood pressure of subjects with plumbism was higher than that of their matched control subjects (137.4±20.2 vs

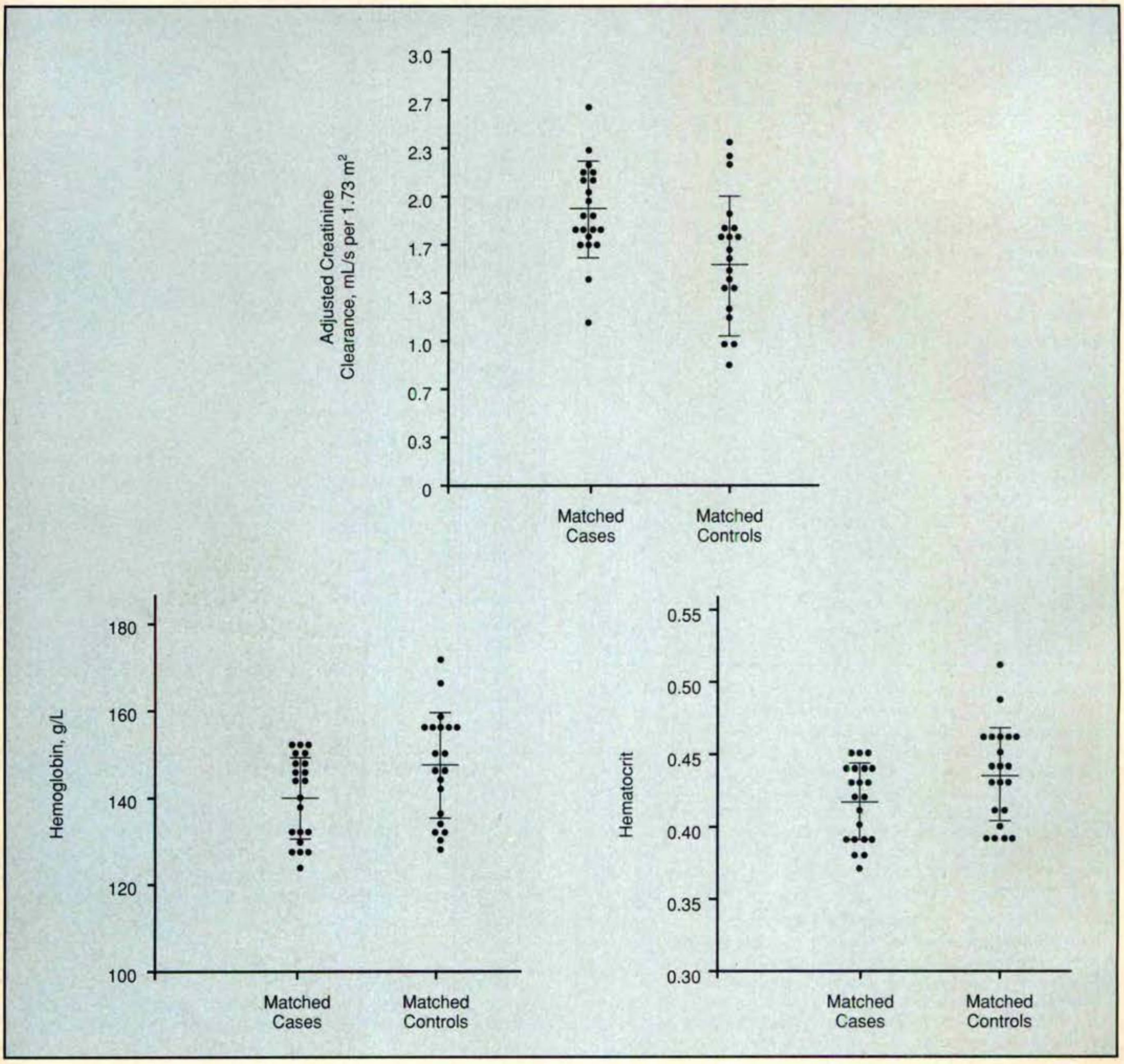

Fig 2.—*Matched subjects with plumbism ("matched cases") vs matched control subjects for selected factors. Bars indicate means with 1 SD.*

132.6±18.9 mm Hg), whereas mean diastolic blood pressure of subjects with plumbism was lower than that of their matched control subject (83.6±9.8 vs 86.4±10.2 mm Hg); however, none of these differences was statistically significant ($P = .36$ and .32, respectively, by paired t tests).

Seven (54%) of the unmatched subjects with plumbism reported taking medications for hypertension. An additional subject who was not receiving medications had elevated blood pressure.

Renal Function, Blood Lead, and Hematologic Variables

One subject with plumbism had grossly abnormal renal function and hypertension with a serum creatinine value of 390 μmol/L and serum urea nitrogen of 24.6 mmol/L. This subject is discussed further below; she and her matched control were eliminated from the following analyses.

Among the remaining 21 matched pairs, no significant difference was noted between subjects with plumbism and control subjects with respect to mean blood lead level, zinc protoporphyrin, serum creatinine, or mean serum urea nitrogen values (Table 3).

Matched subjects with plumbism had a mean adjusted creatinine clearance rate of 1.88 mL/s per 1.73 m², in comparison to control subjects who had a mean rate of 1.48 mL/s per 1.73 m² (Table 3 and Fig 2). The mean expected age- and sex-adjusted creatinine clearance rate for the matched subjects with plumbism and control subjects was calculated from the data of Rowe et al[14] to be 1.57 mL/s per 1.73 m². Nine (41%) of the matched subjects with plumbism and five (38%) of the unmatched subjects with plumbism had creatinine clearance rates above their individual age- and sex-specific 95th percentile predicted values, compared with four (18%) of the matched controls.

Hemoglobin values and hematocrit readings were found to be significantly lower among subjects with plumbism, both male and female (Table 3 and Fig 2). One subject with plumbism and no control subject had values that were below the lower limit that is considered normal for their sex. (Lower limit for male subjects is as follows: hemoglobin, 131 g/L; hematocrit, 0.4; and lower limit for female subjects is as follows: hemoglobin, 115 g/L; hematocrit, 0.37.) No difference was noted in red blood cell size or shape. No significant difference was noted in other biochemical or hematologic factors.

Subject With Frank Renal Failure

The subject with frank renal failure had a history not notable for renal disease until 1973, when at the age of 40 years, during delivery of her eighth and last child, an elevated serum creatinine value and hypertension were discovered. Renal biopsy specimen demonstrated findings consistent with chronic interstitial nephritis. The subject subsequently has been receiving antihypertensive medications and has had slowly progressive azotemia. On this evaluation, her serum creatinine value was 390 μmol/L, with a serum urea nitrogen level of 24.6 mmol/L and creatinine clearance rate of 0.32 mL/s per 1.73 m^2. Her blood lead and zinc protoporphyrin levels were elevated (1.45 μmol/L and 293 μg/dL, respectively). A detailed environmental and occupational history disclosed no identifiable source of ongoing lead contamination. An early morning sample of tap water revealed no evidence of significant lead contamination.

COMMENT

Previous studies of survivors of childhood plumbism concentrated on adults younger than 35 years. Henderson[7] noted that 20 of 101 survivors of plumbism had blood pressures exceeding 140/90 mm Hg. Tepper[8] commented that only one of the 42 survivors of plumbism whom he studied had a blood pressure exceeding 140/90 mm Hg. Moel et al[10] found that systolic blood pressure was higher in survivors of plumbism than in control siblings, but they attributed this to higher weights among the controls. The finding of an elevated risk for hypertension requiring medications among survivors of plumbism in this study of older adults suggests that a latency period of more than 40 years is necessary before this effect occurs.

Bias in the form of selecting subjects who were more likely to have hypertension is unlikely to account for our finding. Follow-up was successful for 76% of the original cohort. Subjects who were targeted for recruitment were chosen based on geographic proximity to the Ambulatory Clinical Research Center. In the recruitment letter, no mention was made of hypertension as an outcome of interest. Matched subjects with plumbism did not differ from matched controls with respect to smoking, alcohol ingestion, education, and body mass index, which militates against confounding by known hypertension risk factors. Moreover, because participating survivors with plumbism had low severity scores, the risk ratio of 7.0 may actually underestimate the risk of hypertension.

Batuman et al[16] found an association between chelatable lead and hypertension that was confined to patients with evidence of chronic renal failure (serum creatinine concentration >130 μmol/L). Other investigators have reported an association of blood lead levels with elevated blood pressure.[5,17-21] By contrast, the subjects with plumbism in our study had neither elevated serum creatinine concentrations nor elevated blood lead levels. Their increased risk of hypertension suggests that remote exposures can cause hypertension in the absence of clinically significant renal disease and discernible elevations in blood lead levels.

The mechanism by which this occurs may depend on subclinical release of bone lead stores into plasma.[22] Bone is the major reservoir of body lead stores in adults and children,[23,24] with a half-life extending for decades.[25,26] It is accepted that while these deposits are readily exchangeable,[4,5,27-29] they can exist without accompanying elevations in blood lead levels.[18,30-32] Campbell et al[33] recently found that men with long-term subclinical lead exposure had increases in the concentrations of plasma renin activity and plasma aldosterone concentrations. In animal studies, lead exposure has been shown to increase sensitivity of vascular smooth muscle via neurogenic and humoral mediators such as catecholamines.[34-36]

As in previous studies in this country, no evidence was found to support renal dysfunction in survivors of plumbism. On the contrary, adjusted creatinine clearance rates for matched subjects with plumbism were unexpectedly found to be significantly high. A similar finding of supranormal creatinine clearance rates was reported by Odutola et al[37] among patients with mild essential hypertension and has been seen among subjects with newly diagnosed diabetes and young diabetics before the onset of proteinuria.[38] In conjunction with increased *p*-aminohippurate clearance rates observed in some experimental studies of lead poisoned rats[39] and clinical studies of lead-toxic workers,[40] these results suggest that lead may actually increase renal blood flow and/or glomerular filtration rates through a shift in autoregulation, perhaps as an intermediate step in the evolution of eventual renal disease. Alternatively, the elevated creatinine clearance concentration could represent enhanced proximal tubular secretion of creatinine as occurs in sickle cell nephropathy.[41]

The single survivor with plumbism who was found to have frank renal failure hints that this outcome may occur, but at a low incidence. Of additional interest is her elevated blood lead level in the absence of an identifiable occupational or environmental source. This may reflect the additive effects of osteoporosis[42] and renal osteopenia in releasing bone lead stores.

This study also found that matched subjects with plumbism had significantly lower hemoglobin and hematocrit values than controls. Although serum iron, folate, and other factors were not measured, the presence of comparable indexes of red blood cell size and shape argues against confounding by common risk factors for anemia. Only one subject with plumbism was mildly anemic (hematocrit, 0.35; hemoglobin, 120 g/L); none had blood lead levels above 0.72 μmol/L. The lowest blood lead level that carries a risk for anemia has recently been estimated to be 0.96 μmol/L.[43] Therefore, the effect observed may represent a subclinical effect of accumulated bone lead stores on hematopoiesis.

As discussed elsewhere, subjects with plumbism differed from controls in other respects as well. Female subjects with plumbism reported a rate of learning disability among their children that was greater than that for female controls.[44] Subjects of both sexes with plumbism performed the cognitive aspects of neuropsychological tests more poorly than controls.[45]

Clearly, another key aspect of the experience of children poisoned by lead is their mortality. Analysis of the 43 death certificates from this study awaits the completion of tracing for a broader cohort of subjects with plumbism; preliminary results suggest an increased mortality rate from renal disease (N. P. Potter, RN, oral communication, September 10, 1990).

CONCLUSION

A high risk of clinically significant hypertension was found developing among 50-year survivors of childhood plumbism in comparison with an age-, sex-, and neighborhood-matched control group. Survivors with plumbism also had lower hemoglobin and hematocrit values. A single survivor with plumbism had frank renal failure that was suspicious of lead nephropathy. Subjects with plumbism were found to have creatinine clearance rates that were significantly greater than controls. The significance of this finding is unclear.

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Brain and Ocular Abnormalities in Infants With In Utero Exposure to Cocaine and Other Street Drugs

Rodrigo Dominguez, MD; Antonio Aguirre Vila-Coro, MD; John M. Slopis, MD; Timothy P. Bohan, MD, PhD

• **We describe 10 infants with developmental delay and congenital cerebral anomalies who were found to have had in utero exposure to vasoactive drugs. Nine infants had ophthalmological abnormalities; these included strabismus, nystagmus, and/or hypoplastic optic discs. Six mothers used cocaine, one used cocaine and heroin, one used only heroin, one used amphetamine, and one used phenylpropanolamine. Each of these cerebral anomalies (agenesis of the corpus callosum, septo-optic dysplasia, schizencephaly, hydranencephaly, congenital hydrocephalus, porencephaly, and cerebral infarctions) can be attributed to insults at different stages of development. There appears to be a relationship between the time of prenatal drug exposure and the type of cerebral anomaly, evoking malformations, disruptions, or fetal strokes. Since many or possibly all of these anomalies are thought to have a vascular origin, it seems appropriate to implicate prenatal exposure to vasoactive drugs.**

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In utero exposure to drugs, particularly street drugs, is a social and medical problem of increasing importance. Although the incidence of heroin abuse has remained relatively constant, the abuse of cocaine has increased sharply in the last few years, in part due to the cheap, highly addictive, smokable form called "crack."[1] The use of crack cocaine during pregnancy is apparently now much more prevalent than the use of other street drugs, including heroin. Some studies in the United States have shown that prenatal exposure to cocaine has affected 11% of these surveyed newborns.[2] The percentage of drug-exposed neonates has apparently quadrupled since 1985.[3] There is a low incidence of in utero exposure to other stimulant drugs, such as amphetamine and methamphetamine.[4] The incidence of prenatal exposure to phenylpropanolamine, which is in diet pills and some decongestants, is unknown.

Cocaine use during pregnancy can have a deleterious effect on both the developing fetus and on the outcome of the pregnancy.[5] The human teratogenicity of cocaine is not well known and is still controversial. Even though one study has stated that cocaine does not cause congenital malformations in humans, most other studies have reported cocaine-induced birth defects[6]; these included congenital genitourinary tract malformations,[7,8] encephalocele, microcephaly, limb anomalies, and bony skull defects.[5,9]

Use of cocaine immediately before and during delivery has been reported to cause cerebral infarction,[10,11] necrotizing enterocolitis,[12] decreased cardiac output,[13] and seizures.[11]

Although some are abnormal, the majority of cocaine-exposed newborns show little or no evidence of drug withdrawal injury during the neonatal period.[14] In contrast, many infants with in utero exposure to heroin often have an abnormal nursery course.[15]

We describe a group of 10 infants who were found to have neurological abnormalities and congenital anomalies of the brain. The cerebral lesions found in our patients included early, middle, and late gestational lesions, thereby further expanding the spectrum of cerebral teratogenicity of cocaine into the early part of pregnancy, which includes cerebral malformations.

METHODS

This study was conducted at the University of Texas Medical School, Houston, from 1987 to middle 1990. We studied seven infants (three females and four males) who presented with strabismus before 6 months of age. The last three infants (two males and one female) presented in the newborn period with abnormal findings from a neonatal neurological examination.

All birth records were obtained and reviewed for maternal and gestational age, delivery history, birth weight, Apgar scores, head circumference, and nursery history. Gestational age was based on the results of newborn examination. Pregnancy history, including prenatal drug use, was obtained from the birth records and, for patients 2 and 4 through 7, from an extensive interview with the mother. The findings from a urine drug screening were abnormal in patients 2 and 8. The remaining eight infants did not undergo screening. All infants underwent screening for neonatal infections. This screening included tests for (1) human immunodeficiency virus (Enzyme Immuno Assay, Abbott Laboratories, North Chicago, Ill); (2) TORCH (*t*oxoplasmosis, *o*ther [syphilis, hepatitis, zoster], *r*ubella, *c*ytomegalovirus, and *h*erpes simplex [maternal infections]) infections (Solid Phase Immuno fluorescence, Whittaker Na Bio Products, Walkersville, Md); and (3) syphilis (rapid plasma reagin charcoal agglutination test, Beckton Dickinson, Mountainview, Calif). All infants were examined by both a pediatric ophthalmologist and a pediatric neurologist. In five patients, the brain anomalies were diagnosed with computed tomography only, in two infants with magnetic

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From the Departments of Radiology (Dr Dominguez), Pediatrics (Drs Dominguez, Slopis, and Bohan), Ophthalmology (Dr Aguirre Vila-Coro), Neurology (Drs Slopis and Bohan), and Pharmacology (Dr Bohan), University of Texas Health Science Center, and the Mann Eye Clinic (Dr Aguirre Vila-Coro), Houston.

Reprint requests to Department of Radiology, University of Texas Health Science Center, 6431 Fannin, Room 2.132 MSB, Houston, TX 77030 (Dr Dominguez).

Table 1.—Pregnancy, Labor, and Delivery History of Infants With In Utero Drug Exposure

Infant	Gestation, wk	Weight, g	Head, cm	Maternal Age, y	Delivery	Nursery Course	Prenatal Care	In Utero Drug Exposure*
1	40	2810	31.8†	24	Spontaneous delivery	Normal nursery course of 2 d	Some prenatal care	IV cocaine use during first 7 mo
2	27	1070	28	25	Cesarean section for fetal distress	Long course due to prematurity	None	Amphetamine use during most of the pregnancy
3	39	2930	30.5†	28	Precipitous delivery	Normal nursery course of 3 d	Some prenatal care	IV cocaine use during most of the pregnancy
4	40	3068	31.8†	26	Spontaneous delivery after only 2 h of labor	Normal nursery course of 2 d	None	Use of diet pills containing phenylpropanolamine during 6-12 wk
5	38	3350	33	24	Spontaneous delivery	Normal nursery course of 3 d	None	IV heroin use during most of the pregnancy, but no use of cocaine
6	40	4005	31.8†	20	Spontaneous delivery	Normal nursery course of 5 d	Some prenatal care	Crack cocaine use during 1st and 2nd trimester
7	39	3660	36.5	34	Delivery induced due to pregnancy-induced hypertension	R clavicle fracture but otherwise normal nursery course of 2 d	Some prenatal care	IV cocaine and heroin use during 3-8 mo
8	40	2480	32†	24	Precipitous delivery	Complicated by late-onset meningitis	Some prenatal care	Crack cocaine use during most of the pregnancy
9	32	1500	27	35	Spontaneous delivery after premature rupture of membranes	Respiratory distress, seizures, and congenital syphilis that did not involve the brain	None	IV cocaine use throughout pregnancy
10	38	2370	31†	17	Spontaneous delivery	Neonatal seizures	None	In utero cocaine during 1st and 2nd trimester

*IV indicates intravenous.
†Microcephalic—head circumference more than 2 SDs below the mean for gestational age.

resonance imaging only, and in another infant with neonatal head ultrasound only; two patients were studied with both magnetic resonance imaging and computed tomography.

RESULTS

Prenatal and Perinatal Histories

The pregnancy, labor, and delivery histories of the 10 patients are summarized in Table 1; of the 10 infants, three were adopted. Seven infants were delivered vaginally at full term, and two were premature. One was born by cesarean section due to fetal distress. All infants had normal Apgar scores; seven had a normal nursery course. Six of the 10 infants were microcephalic. All infants had had prenatal exposure to vasoactive drugs, ie, cocaine, heroin, amphetamine, or phenylpropanolamine. For all patients, the drug exposure occurred during at least part of the first trimester, and in four patients, it occurred throughout most of the pregnancy. The mother of patient 4 did not know that she was pregnant when she consumed phenylpropanolamine diet pills during part of the first trimester. The remaining nine mothers were long-term drug addicts, and it was not possible to quantitate accurately their drug intake. All infants had normal karyotypes, and except for patient 9, negative titers for common congenital infections, including human immunodeficiency virus, toxoplasmosis, rubella, cytomegalovirus, syphilis, and herpes simplex. Although patient 9 had congenital syphilis, the results of his cerebrospinal fluid studies were normal, and hence, he did not have neurosyphilis.

In two infants (patients 2 and 8), cocaine was detected in the urine at birth. Patients 1, 2, and 10 had abnormal neurological findings at birth, and their mothers admitted to the use of cocaine during pregnancy. The remaining seven infants were identified later because of their unusual ophthalmological anomalies and were found to have a history significant for drug exposure.

Neurological and Ophthalmological Findings

The neurological and ophthalmological findings are summarized in Table 2. All infants were examined by a pediatric neurologist (T.P.B. or J.M.S.). For some patients, this assessment included a Denver Developmental Assessment and/or a Bayley Neuropsychiatric Assessment of mental and motor performance. All infants had some degree of global developmental delay, that is, a delay in both mental and motor skills. Although the types of abnormalities were similar, the severity varied. Except for the three infants who were examined in the newborn period, distal hypertonicity and some degree of spasticity were consistent features.

Another feature that was found in all patients was truncal ataxia. In the younger infants, this was manifested by poor head control and axillary slippage. Some of the older

Table 2.—Neurologic and Ophthalmologic Findings at Time of Presentation in Infants With In Utero Drug Exposure

Infant/Age, mo	Primary Caretaker*	Neurologic Findings	Ophthalmologic Findings
1/5½	AM	Truncal ataxia, spastic diplegia, L hemiparesis, history of facial seizures, global delay	Intermittent esotropia and hypoplastic optic discs bilaterally
2/Newborn	BM	Motor delay with truncal hypotonia	No apparent strabismus but patient did not have adequate fixation for evaluation, normal funduscopic examination results
3/3	AM	Global delay with truncal ataxia, swallowing difficulties, severe hypertonia with opisthotonic posturing and seizures	Optokinetic nystagmus absent, bilateral disc atrophy with apparent blindness
4/3½	AM	Global delay with truncal ataxia, distal spasticity, hypertonicity, opisthotonic posturing	Incomplete L 3rd nerve palsy with partial ptosis; minimally reactive pupil, exotropia, and vertical nystagmus of the R eye; normal optic discs
5/3	BM	Global delay with truncal ataxia, severe hypertonicity, spasticity, poor head control	Exotropia of 65° with full ductions and versions, subtotal cupping of the L optic disc with spontaneous pulsations of the L central retinal artery
6/6	BM	Global delay with truncal ataxia and distal spasticity, hypertonicity, reduced interactions with environment	Bilateral exotropia of 35° with full ductions and versions
7/4	BM	Global delay, truncal ataxia with distal spasticity and hypertonicity	Variable exotropia of 40-90° with full ductions and versions, fine pendular nystagmus
8/Newborn	BM	Global delay, with seizures	Intermittent esotropia
9/11	BM	Global delay with truncal hypotonia, poor head control, inability to sit, distal hypertonicity	Absent upgaze, poor visual fixation and following, normal funduscopic examination results
10/Newborn	BM	Motor delay with diffuse hypotonia, particularly truncally	Nystagmus with normal fundi

*AM indicates adoptive mother; BM, biologic mother.

infants had achieved head control, but the axillary slippage had not resolved. Patients 1 and 9 were followed up until the 13th and 18th months, respectively, and both had truncal ataxia; this last infant, patient 9, was unable to sit and still had poor head control; and patient 1 had poor sitting posture and was unable to stand without holding on. At 18 months of age, he was about 6 months delayed. Two patients were profoundly delayed. Patient 6 has been bedridden, receiving gastrotomy feedings, and has not achieved any significant developmental milestones. Patient 5 never achieved any developmental milestones and died of pneumonia at 11 months of age. Seizures occurred in five patients; two infants (patients 9 and 10) had transient neonatal seizures, and patient 1 had a single seizure at 6 months of age. Two patients had chronic seizures.

Nine infants had ophthalmological abnormalities. Strabismus was a consistent finding in all infants in whom adequate visual fixation had developed. Adequate visual fixation had not yet developed in infants 2 and 10. Five infants had exotropia, two had esotropia, one had absent upgaze, two had nystagmus, and one had a unilateral third nerve palsy. Two patients were apparently blind. Four patients were followed up for many months, and the eye findings were persistent. By 18 months, patient 1 had some reduction in the angle of the esotropia. The absent upgaze persisted in patient 9; patient 5 died; and patients 6 and 7 had corrective surgery for their strabismus. Three infants also had abnormal optic discs.

Neuroimaging

The anatomical findings of the 10 patients who were under study are described in Table 3 according to the presumed time of insult during pregnancy. These anomalies included midline cerebral malformations (eg, septo-optic dysplasia), errors of neuronal migrations (eg, dysgenesis of the corpus callosum and schizencephaly), disruptions (hydranencephaly, "congenital" hydrocephalus, and porencephaly), or perinatal strokes (Figs 1 through 4). Magnetic resonance imaging, when available, allowed a clearer assessment of the abnormalities due to its inherent properties as follows: better resolution, contrast sensitivity for soft tissues, and multiplanar-imaging capabilities.

Prevalence

Due to the retrospective nature of our study, we could only estimate the prevalence of these cerebral malformations. Two types of estimates were possible: (1) the prevalence of these cerebral malformations in drug-exposed infants and (2) the prevalence of cerebral malformations in infants with drug-induced strabismus. Of the 10 patients described here, five were born at Hermann Hospital, Houston, and one was born at an outlying hospital; they were studied during infancy. The other four infants were born at the new county hospital (Lyndon B. Johnson General, Houston). Three infants were studied in the nursery, and one was studied at 11 months of age. Although the last institution had been open for 16 months, it has only been a University of Texas facility since July 1, 1990. The three newborns in the study were discovered among the

Table 3.—Neuroimaging: Anatomical Findings of the Six Patients Under Study According to the Time of the Vascular Insult During Intrauterine Life*

	Time of Gestational Insult			
Infants	**Trimester**	**Week**	**Type of Lesions/Malformations**	**Radiological Findings(CT and/or MRI)**
1 and 2	1st	7	Dysgenesis of the corpus callosum†	Absence of corpus callosum, parallel and widely spaced lateral ventricles, frontal horns narrowed, occipital horns enlarged (colpocephaly), 3rd ventricle in continuity with interhemispheric fissure anteriorly
3	1st	7½	Septo-optic dysplasia with schizencephaly†	Bilateral open-lips schizencephaly with heterotopic gray matter lining lips; both corpus callosum and septum pellucidum are absent
4	1st	7½	Septo-optic dysplasia with schizencephaly†	Bilateral closed-lips schizencephaly at junction of frontal and parietal lobes with thin clefts of subarachnoid space lined by gray matter extending to ventricular margins; septum pellucidum is absent; corpus callosum and optic nerves are hypoplastic
5	2nd	12-24	Encephaloclastic hydranencephaly‡	Replacement of cerebral cortex by CSF-filled sacs with residual occipital lobe and preservation of basal ganglia, cerebellum, and falx
6	2nd	13-14	Porencephaly of 2nd trimester with midline brain anomalies‡	Large porencephalic cavity confluent with R lateral ventricle and replacing most of the R brain mantle, septum pellucidum is absent
7	3rd	28-32	Porencephaly with normal midline structures§	Bilateral wedge-shaped porencephalic cavity at parietal lobes, moderate cerebral atrophy and asymmetrical enlargement of R lateral ventricle
8	3rd	28-32	Porencephaly with normal midline structures§	Microcephaly, mild brain atrophy, noncommunicating hydrocephalus, extensive cerebral infarctions, small bilateral porencephaly
9	3rd	28-32	Porencephaly with partially destroyed normal midline structures§	Noncommunicating hydrocephalus, fenestration of septum pellucidum and thinned-out corpus callosum, large porencephalic cyst at R occipital lobe
10	3rd	36	Bilateral posterior cerebral infarcts§	Diffuse decreased density within cerebral hemispheres affecting mainly deep white matter and most prominently in parieto-occipital watershed areas, mild associated edema with compression of lateral ventricles

*CT indicates computed tomography; MRI, magnetic resonance imaging; and CSF, cerebrospinal fluid.
†Malformation only.
‡Malformation and disruption.
§Encephaloclastic lesion.

2510 infants who were born during these 3 months. Although that hospital does not screen all newborns, limited surveys at that institution suggest that 10% to 15% of the infants have had prenatal exposure to drugs of abuse. We therefore estimate that 250 to 375 of these infants have had prenatal exposure to drugs. We would further estimate that 0.8% to 1.2% of infants with prenatal drug exposure have congenital malformations of the brain. This is probably an underestimation since at that hospital neuroimaging is only done on children with (1) a head of abnormal size or shape or (2) a neurological abnormality, such as a seizure.

Of the 10 infants described here, all but patients 2 and 10 had strabismus. At the time of examination, neither patient had adequate fixation for full evaluation. During the first year covered in this study, our pediatric ophthalmologist (A.A.V.-C.) examined 200 infants with strabismus who were younger than 6 months of age. One hundred ninety-two infants had the much more common condition of infantile congenital esotropia; only eight infants suffered from congenital exotropia, including the four patients who constituted the starting point of our research. The rarity of congenital exotropia[16] and the obvious developmental delay in these four infants led to neuroimaging and neurological evaluation. The findings in these first four patients prompted the remainder of this study.

COMMENT

In the present study, we have reported congenital ocular abnormalities and congenital brain malformations in infants with prenatal exposure to cocaine and/or other vasoactive drugs. Three of these patients had been described previously.[17] Specific cerebral abnormalities that have been associated with maternal cocaine and methamphetamine exposure are perinatal strokes and intracranial hemorrhages, intracerebral cysts,[4,10] exencephaly, bony skull defects, and microcephaly[18] with brain atrophy.[4,5] The strokes and hemorrhage were related to drug exposure during the latter part of the third trimester, and no comment was made about ocular abnormalities. The other anomalies (exencephaly and bony skull defects) would have been related to earlier, probably first-trimester drug exposure.

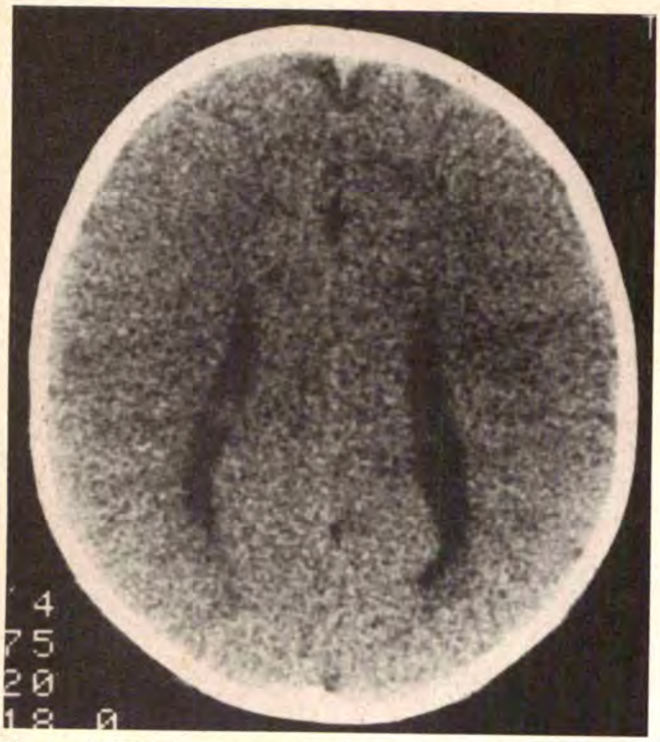

Fig 1.—*Patient 2. Dysgenesis of the corpus callosum. Axial noncontrast-enhanced computed tomographic scan of the brain at the level of the bodies of the lateral ventricles. Note the parallel widely spaced lateral ventricles with narrowing and a characteristic lateral convexity of their frontal horns (due to the formation of the hemilateral bundles of Proust, secondary to the absence of corpus callosum). The fibers that course parallel to the hemispheric fissure indent the medial wall of the lateral ventricles (arrowheads).*

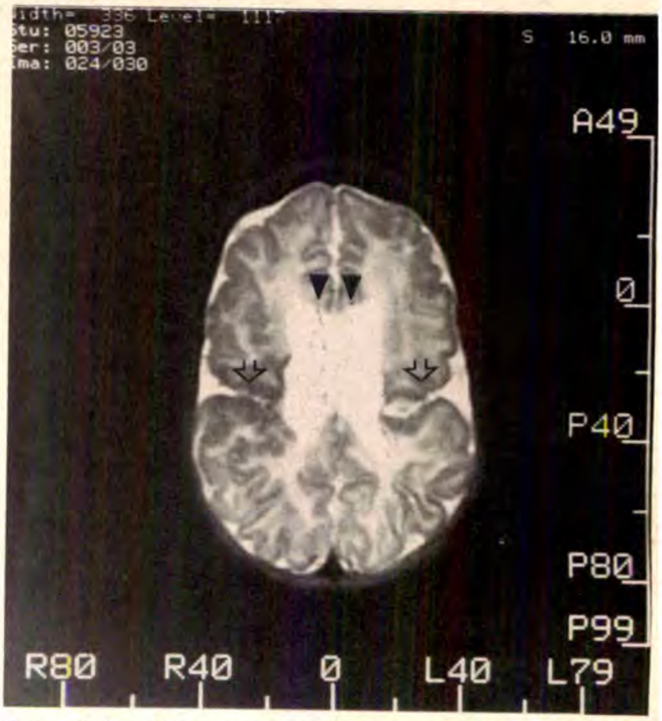

Fig 2.—*Patient 5. Septo-optic dysplasia and schizencephaly. Axial T_2-weighted magnetic resonance imaging of the midbrain at the level of the lateral ventricles. The ventricles communicate freely due to the absence of septum pellucidum; note the shallow anterior and medial margins of the lateral ventricles secondary to the hypoplasia of the corpus callosum (arrowheads). Bilateral closed-lips schizencephaly at the junction of frontal and parietal lobes (open arrows). These thin clefts of the subarachnoid space extend into the ventricular margins. Note, in this magnetic resonance imaging sequence, the dark band of heterotopic gray matter that rims the clefts, as proof of the abnormal neuroblastic migration.*

Other nonneurological effects of prenatal cocaine include spontaneous abortion, abruptio placentae, prematurity, intrauterine growth retardation,[5,9] stillbirth,[18] and neurobehavioral problems.[14] Studies of infants with prenatal exposure to cocaine also reveal a significant incidence of strabismus[19] and congenital microcephaly.[4,5] The lesions that were found in our patients included early, middle, and late gestational lesions, thereby further expanding the spectrum of cerebral teratogenicity of cocaine into the early part of pregnancy.

There have been only a few animal studies of cocaine teratogenicity, and these have produced conflicting results, possibly due to species variability. In CF-1 mice, cocaine produced significant ocular abnormalities, ranging from frequent anophthalmia to lens hypoplasia and microcephaly.[20] In one study of Sprague-Dawley rats, there were significant limb malformations but no anophthalmia.[21] In another study of Long-Evans rats, only one of 360 rat embryos had anophthalmia.[22] The animal studies and human epidemiology seem to indicate that the risk of severe anatomical malformations from cocaine is dose dependent but low.[23] The absence of cerebral malformations in most other studies of cocaine-exposed infants may be due to a combination of the small size (<100 patients) of most studies and the low prevalence (our estimate, 0.8% to 1.2%) of the malformations in drug-exposed infants. In fact, in the one large study, there was a significant incidence of cerebral malformations in cocaine-exposed neonates.[24]

Although some congenital malformations of the brain are associated with strabismus,[25] to our knowledge, there have been no reports that link the prenatal, drug-induced strabismus to cerebral malformations. Strabismus, nystagmus, and ocular torticollis are often found in infants with in utero exposure to heroin, methadone, and/or cocaine, but these abnormalities are often not appreciated until several months of age,[19,26,27] and they have never been correlated with cerebral anomalies. In addition to strabismus, prenatal exposure to cocaine can also cause other ocular abnormalities. These include optic nerve hypoplasia, retinal colobomas, and micro-ophthalmia with retinal dysgenesis.[28]

Similarly, congenital microcephaly is associated with cerebral malformations,[29] but, to our knowledge, there have been no reports that link prenatal, drug-induced microcephaly to cerebral malformations. To date, neurobehavioral problems are the major reported complications of prenatal cocaine exposure.[14]

Cocaine-induced vasoconstriction can occur in all organs, including the placenta,[30] heart,[31] and brain.[32] Cocaine-induced vasoconstriction in the brain can cause strokes and intracranial hemorrhages.[33] Amphetamine and phenylpropanolamine, an anorexic agent that is chemically similar to amphetamine, are both potent vasoconstrictors.[34] Like cocaine, both have also been reported to cause strokes and intracranial hemorrhages.[35] Although less well known, heroin has also been reported to affect cerebral blood flow in humans and cause cerebral anoxia.[36,37] Its actions are presumably mediated via stimulation of endorphinergic systems. Several animal studies also indicate that endorphinergic systems are involved in regulating cerebral blood flow.[38,39]

The congenital anomalies that were present in our patients fall into three categories. In the first category are

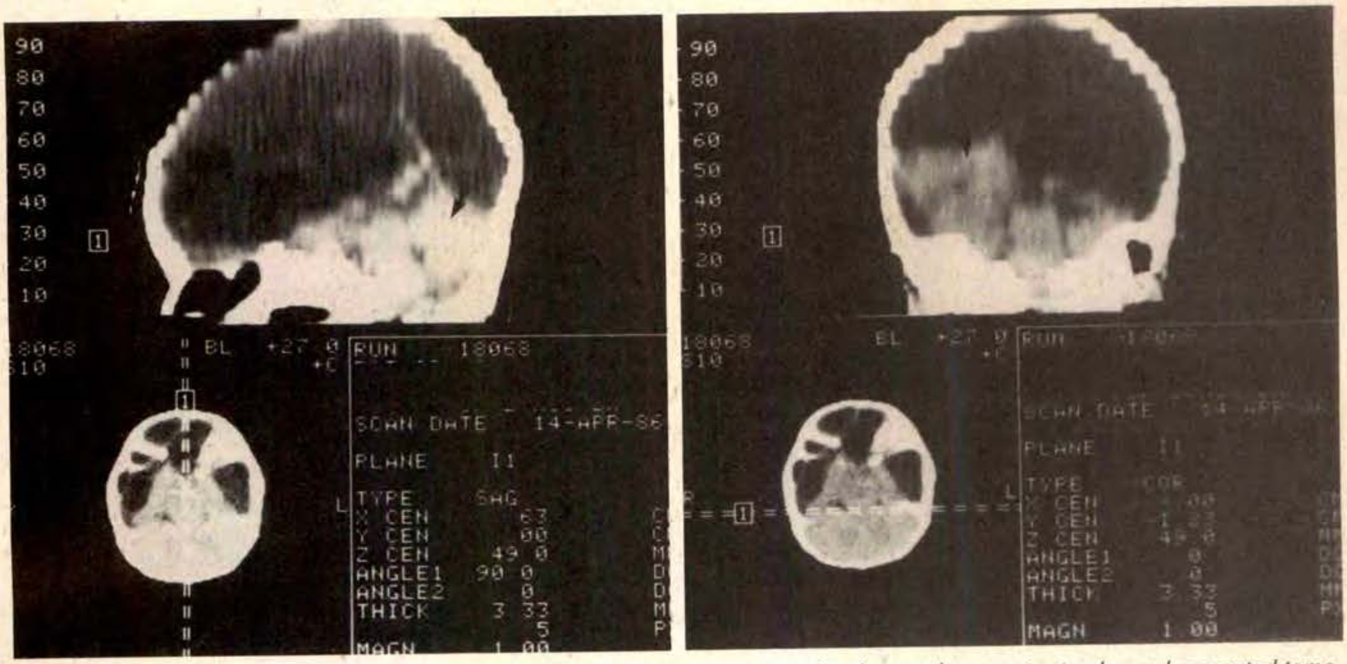

Fig 3.—*Left and right, Patient 7. Hydranencephaly. Midline sagittally reconstructed and coronal noncontrast-enhanced computed tomographic scan planes of the brain reveal incomplete replacement of the cerebral cortex with cerebrospinal fluid–filled sacs. Note the presence of residual occipital cortex and the preservation of the basal ganglia and cerebellum (arrows).*

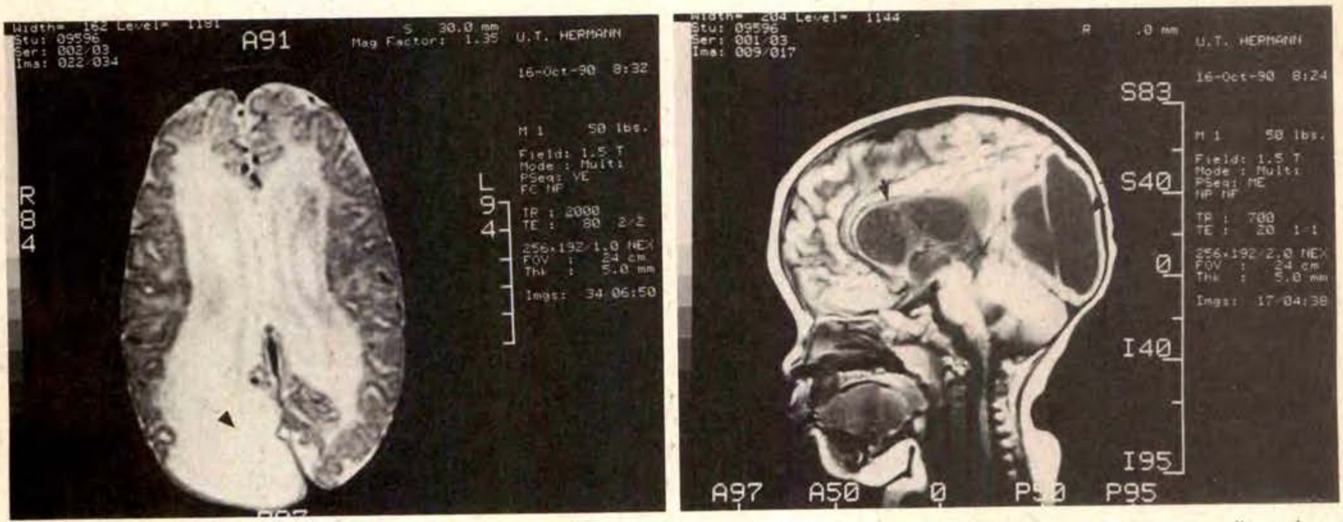

Fig 4.—*Patient 10. Porencephaly. Sagittal (left), T_1-weighted and axial (right), T_2-weighted magnetic resonance imaging revealing a large porencephalic cyst (arrowhead) at the right occipital lobe illustrated on both the sagittal (left) and axial (right) image. Also note the communicating hydrocephalus. Note the preservation of the midline brain structures, although the ventricular dilatation has thinned out the corpus callosum (arrow on left) and fenestrated the septum pellucidum right (open arrow).*

dysmorphic lesions in which the insult occurred at an early (5 to 7 weeks) stage of embryogenesis. During this time period, ventral induction in the cephalic end of the central nervous system takes place with differentiation of midline brain structures, such as the optic vesicles and retinal ganglion cells; the anterior wall of the diencephalon then forms the commissural plate and septum pellucidum.[40] Our patients' malformations in this category included agenesis of the corpus callosum, septo-optic dysplasia, and schizencephaly (patients 1 through 4). These malformations may be seen alone or in association with each other[41] and/or with hypoplasia of the optic nerves.[42] The results of this and other studies[28,43] support the hypothesis that a hypotensive insult or ischemic event is the cause for this group of anomalies. Although the authors do not make this point, the results of the study by Skarf and Hoyt[42] support linkage of septo-optic dysplasia to a vascular event. They reported the neuroanatomical and neurologic findings in patients with optic nerve hypoplasia. One group in their study consisted of 41 infants with bilateral optic nerve hypoplasia and nystagmus. Three of these 41 patients also had a porencephalic cyst, a lesion that is known to have a vasogenic origin; unless there is one cause for the optic nerve hypoplasia and another for the porencephalic cyst, one has to conclude that, in these three patients, the two lesions had the same, that is, a vascular origin. The vascular origin of septo-optic hypoplasia is also supported by the findings from the recent report of three cocaine-exposed infants with retinal abnormalities, including both optic nerve hypoplasia and retinal dysgenesis; one of the three infants also had a cerebral malformation.[28] Furthermore, three additional patients in the study of Skarf and Hoyt[42] had an encephalocele, a lesion that others have found in infants with prenatal cocaine exposure.[18,24]

Although it is somewhat hypothetical, one could extrapolate from the cocaine-induced anophthalmia report in CF-1 mice[20] to cocaine-induced septo-optic dysplasia in humans. One would hypothesize that septo-optic dysplasia, micro-ophthalmia, and anophthalmia are different points on a continuum, and that an agent that caused anophthamia in one species could cause septo-optic dysplasia in another. This hypothesis is supported by the findings from the recent report of cocaine-exposed infants with optic nerve hypoplasia and micro-ophthalmia.[28]

The second category of lesions are due to an insult that occurs somewhat later in gestation, toward the end of the first trimester, which is a borderline period between late brain malformation and disruptive pathophysiological mechanisms.[44] Lesions in this category include a spectrum of disruptions or destructive anomalies that range from hydranenchephaly to porencephaly and congenital hydrocephalus. In hydranenchephaly (patient 5), there is a nearly complete destruction of the cerebral hemispheres, which are replaced by cerebrospinal fluid–filled sacs.

Porencephaly is understood as a large hemispheric defect that communicates with one of the lateral ventricles. Porencephalic defects that are due to second-trimester insults are located in the territory of the middle cerebral artery, extend across the entire thickness of the cerebral mantle, and are often associated with absence of the septum pellucidum[45] (as in patient 6). In contrast to schizencephaly, porencephalic defects are not lined with gray matter.

In the third category are another type of porencephalic cysts (patients 7 through 9). These do not necessarily involve the entire thickness of the cerebral mantle and are often associated with some degree of homolateral or diffuse cerebral atrophy.[45] The septum pellucidum is usually present. These are also referred to as perinatal strokes.

In some, but not all, of the infants described here, there appeared to be a correlation between the time of prenatal drug exposure and the type of lesion (Tables 1 and 3). Patient 4, who was exposed to phenylpropanolamine during the sixth to 12th weeks, had schizencephaly, a lesion consistent with an early dysmorphic insult. The porencephalic cysts in patient 6 were consistent with an insult during the second but not the third trimester of pregnancy. This patient had exposure to cocaine during the first and second trimesters but not the third trimester. The porencephalic cysts in patients 7 through 9 were consistent with a third-trimester insult, and these patient's mothers consumed cocaine well into the third trimester. Such a correlation is not always possible since many infants are exposed to drugs throughout much of the pregnancy. Additionally, the polydrug abuse that is common in many addicts makes it more difficult to understand the specific effects of maternal street drug consumption. As was the case with three of our patients, these pregnant women often give up their infants for adoption and leave no records of perinatal drug use. Even in infants who are not adopted, the social taboo and the legal complications of admitting drug abuse during pregnancy increase the likelihood of false-negative clinical histories. The presence of congenital strabismus (particularly exotropia), a vascular dysencephaly, and/or congenital microcephaly appear to be an indication to search for a history of prenatal drug exposure. A drug screening with normal results at birth obviously does not exclude significant prenatal drug exposure, and in fact, four of our 10 mothers stopped drug use 1 or more months before delivery. Since cocaine causes vasoconstriction, the presence of either placental or neonatal infarctions in the cerebrum or viscera should also prompt a careful history of prenatal drug exposure.

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A Preliminary Report of Prenatal Cocaine Exposure and Respiratory Distress Syndrome in Premature Infants

Barry Zuckerman, MD; Edward C. Maynard, MD; Howard Cabral, MPH

• A prospective study of maternal drug use during pregnancy and newborn outcomes provided us with an opportunity to assess the relationship between prenatal cocaine use and respiratory distress syndrome among premature infants. Women were consecutively recruited from the prenatal clinics at Boston (Mass) City Hospital between 1984 and 1988 and were interviewed during the prenatal and postpartum period by trained bilingual interviewers. Urine specimens were collected at the time of each interview and were analyzed for marijuana and cocaine metabolites. Following delivery, one of five pediatricians who were "blinded" to the mothers' prenatal and drug history performed a physical examination and abstracted medical information, including the diagnosis of respiratory distress syndrome from the medical record. The study sample consisted of 33 infants born at 34 weeks' or less gestation who were appropriate for gestational age and not exposed to heroin or methadone prenatally. Eight of the mothers of these 33 infants used cocaine prenatally. One (12%) of eight cocaine-exposed infants was diagnosed as having respiratory distress syndrome compared with 13 infants (56%) not exposed to cocaine prenatally. Infants not exposed had an odds ratio of 8.9 (95% confidence interval: 0.9, 83.5) for respiratory distress syndrome compared with infants exposed to cocaine prenatally. When the analysis was controlled for prolonged rupture of membranes, black race, infant gender, or gestational age, the adjusted odds ratio was essentially unchanged. This preliminary observation of a decreased incidence of respiratory distress syndrome among premature infants prenatally exposed to cocaine appears to be biologically plausible and needs to be confirmed in future studies with larger numbers of subjects to control for potentially confounding variables.

(*AJDC*. 1991;145:696-698)

In 1970, it was first noted that premature infants of mothers addicted to heroin have a low rate of respiratory distress syndrome (RDS).[1] During the past 5 years, cocaine has become a much more common drug of abuse, with one study[2] showing that 18% of women receiving prenatal care used cocaine during pregnancy. Published reports show numerous adverse outcomes, including low birth weight, microcephaly, and prematurity, are associated with cocaine use during pregnancy.[2-7]

However, little is known about the relationship between prenatal cocaine use and RDS. It is striking that published reports showing rates of prematurity ranging from 24% to 51% have consistently failed to mention RDS as an adverse neonatal outcome in infants born to mothers using cocaine.[3-5] One retrospective case-control study reported a lower rate of RDS among cocaine-exposed premature infants.[8] As part of a larger study of maternal drug use during pregnancy and newborn outcomes,[2] we investigated the relationship between maternal use of cocaine during pregnancy and RDS among the subsample of premature infants.

SUBJECTS AND METHODS

Recruitment of Subjects

Subjects were consecutively recruited at the Women's and Adolescent Prenatal Clinics at Boston (Mass) City Hospital from July 1984 through June 1987. English-speaking and Spanish-speaking women who were willing to give informed consent and who gave birth by December 31, 1987, were eligible to participate in the study. The protocol was approved by the Human Studies Committee of Boston City Hospital. Subjects were protected from the use of data for criminal prosecution by a Writ of Confidentiality under Title 42 of US Code Section 242A. To minimize unavailability for follow-up, participants were paid $10 for each interview.

Assessment of Participants

All participants were interviewed twice, once during the prenatal period and again during the postpartum period, by trained bilingual interviewers. A close-ended, forced-choice interview elicited the timing and frequency of the use of cocaine, marijuana, cigarettes, alcohol, and other illicit psychoactive substances before and during pregnancy. The interviewers were unaware of the results of the infant assessments conducted by the study pediatricians.

Participants were asked to submit urine samples at the time of each interview and were informed that their urine would be assayed for "marijuana and prescription and nonprescription drugs" and that the results would remain confidential and not become part of their clinical record. Urine samples to identify cocaine were obtained from the mother and not the infant during the postpartum period. Women were classified as cocaine users if their urine sample was positive for metabolites of cocaine or if, at either interview, they reported using cocaine during pregnancy. All urine samples were screened for benzoylecgonine, the major metabolite of cocaine, by enzyme-mediated immunoassay

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From the Division of Developmental and Behavioral Pediatrics, Department of Pediatrics, Boston (Mass) City Hospital/Boston University School of Medicine (Dr Zuckerman and Mr Cabral), and the Department of Pediatrics, University of Massachusetts Medical School (Dr Maynard), Boston.

Reprint requests to the Division of Developmental and Behavioral Pediatrics, Boston City Hospital, Talbot 214, 818 Harrison Ave, Boston, MA 02118 (Dr Zuckerman).

Table 1.—Comparison of Maternal Characteristics Between Women Who Used and Did Not Use Cocaine During Pregnancy (N = 33)

	Cocaine Use, %		
	Nonuse (n = 25)	Use (n = 8)	*P*
Black race	72	75	.62
Cigarette use	36	100	.002
Alcohol use	48	75	.18
Pregnancy-induced hypertension	28	38	.83
Prolonged ROM (>12 h)*	20	50	.12
Abruptio placentae	12	25	.93

*Clinical standard used at Boston (Mass) City Hospital during the study years to indicate increased suspicion for neonatal sepsis. ROM indicates rupture of membranes.

Table 2.—Comparison of Characteristics Between Infants of Mothers Who Used and Did Not Use Cocaine During Pregnancy (N = 33)*

	Cocaine Use, %		
	Nonuse (n = 25)	Use (n = 8)	*P*
Birth weight, g	1554 (730)	1577 (225)	.89
Gestational age, wk	31.1 (2.2)	32.3 (1.1)	.18
Male gender	46	50	.73
Apgar Score at 1 min	5.6 (2.8)	5.5 (2.7)	.90
Apgar score at 5 min	7.0 (2.2)	7.6 (2.0)	.50
RDS	56	13	.03

*Values are mean (SD) or percent. RDS indicates respiratory distress syndrome.

technique (Syva Co, Palo Alto, Calif). When sample volume permitted, presumptive positive samples were confirmed by gas chromatography/mass spectrometry. If specimen volume was insufficient, a second enzyme-mediated immunoassay technique assay performed on a different day was used as a confirmatory test.

Following delivery, one of five pediatricians who were "blinded" to the mothers' prenatal and drug history performed a standard physical examination. Gestational age was determined according to the method of Dubowitz et al.[9] After performing the physical examination, the study pediatrician reviewed the infants' medical records to ascertain the Apgar scores and intrapartum and perinatal complications. The clinical staff of the neonatal intensive care unit diagnosed RDS by clinical symptoms and chest roentgenogram. This information was abstracted from Boston City Hospital's problem-oriented medical record by the study pediatrician. A more complete description of the methods and quality control for urine assays has been published elsewhere.[2]

Statistical Analysis

Bivariate analyses for categorical data were performed with the χ^2 test and Fisher's Exact Test. Means of continuous variables were compared for users and nonusers of cocaine by *t* tests. Unadjusted and adjusted odds ratios and 95% confidence intervals were calculated from logistic regression models[10] assessing the relationship of cocaine use and RDS.

RESULTS

The study sample consisted of 38 infants who were born at 34 weeks' gestation or less. Infants with intrauterine growth retardation (n = 1) and opiate (heroin and/or methadone) exposure during pregnancy (n = 2) were excluded from the analysis because these conditions are known to be associated with a lower rate of RDS. The research records of two additional infants did not indicate whether RDS was present or absent, leaving a final sample size of 33.

The mean (SD) gestational age of the study sample was 31.4 (2.0) weeks, and mean (SD) birth weight was 1560 (641) g. Forty-five percent of the infants were male. Most of the infants were black (67%), 15% were white, 6% were Hispanic, and 12% were other. Fourteen infants (42%) had RDS. During the years the study was conducted, all mothers with impending delivery between 26 and 36 weeks' gestation received steroids; no infant was treated with surfactant.

Eight of the 33 women used cocaine prenatally. Mothers who used cocaine were similar to those who did not, except that cocaine-using mothers were younger (19.9 [0.8] years vs 26.3 [6.3] years, $P < .001$) and more likely to smoke cigarettes (Table 1). Of the eight cocaine users, three reported using less than once a month, two reported using one to two times a week, and three reported using three or more times a week. Two of the eight cocaine users had a positive urine assay for cocaine metabolites.

The mean birth weight and the mean gestational age of the cocaine-exposed infants were not significantly different from of those of infants not exposed (Table 2). One (12%) of eight cocaine-exposed infants was diagnosed as having RDS compared with 13 infants (56%) not exposed to cocaine prenatally ($P = .03$). Infants not exposed had an odds ratio of 8.9 (95% confidence interval: 0.9, 83.5) for RDS compared with infants exposed to cocaine prenatally. When the analysis was controlled for prolonged rupture of membranes, black race, infant gender, or gestational age, the adjusted odds ratio was essentially unchanged.

COMMENT

Our preliminary investigation suggests that RDS occurs significantly less frequently among premature infants prenatally exposed to cocaine compared with premature infants not so exposed. The findings are similar to those previously reported in a retrospective case-control study, which found RDS in four (25%) of 16 cocaine-exposed infants vs 20 (63%) of 32 controls.[8] To our knowledge, this preliminary report represents the first prospective investigation of prenatal cocaine exposure that has evaluated RDS as an outcome. The relatively small numbers of subjects born at less than 34 weeks' gestation during the 3-year period is in part due to the exclusion of women who did not receive prenatal care; subject recruitment only occurred during prenatal care. While the sample size is small and we do not have information regarding the amount and duration of mechanical ventilation, the strength of our study is that cocaine use was ascertained prospectively both during pregnancy and post partum. The use of both self-report and urine assay is important to identify prenatal cocaine use. In a previous study, had we relied solely on self-report, we would have missed 24% of cocaine users who would have then been misclassified as nonusers.[2] In this study, had we not conducted interviews, we would have missed six of the eight mothers who used cocaine prenatally.

There are several possible mechanisms to explain this observation. Cocaine causes maternal hypertension and decreased uterine blood flow,[11] both of which have been associated with accelerated fetal lung maturation as assessed by amniotic fluid phospholipid analysis.[12] This effect is probably mediated by fetal glucocorticoids that affect surfactant synthesis.[13] Fetal catecholamines may also contribute to accelerated fetal lung maturation by increasing synthesis and secretion of surfactant.[14] Elevated norepinephrine levels among 2-month-old infants[15] and elevated levels of norepinephrine precursors[16] among newborns have been shown in infants born to mothers using cocaine during pregnancy. This increase may be a direct effect of cocaine, which blocks presynaptic reuptake of norepinephrine and epinephrine or a result of adrenal catecholamine release in response to fetal hypoxia secondary to uterine vasoconstriction. Other mechanisms for an effect of cocaine on the developing lung are also possible, as suggested by studies implicating endogenous opioids in fetal lung maturation.[17]

This preliminary observation of a decreased incidence of RDS in cocaine-exposed premature infants appears to be biologically plausible. In fact, data have recently been reported that demonstrate accelerated fetal lung maturation in rabbits following in utero exposure to cocaine.[18] This clinical observation in newborns needs to be confirmed in future studies with an adequate number of subjects to control for other factors known to influence the incidence of RDS, such as intrauterine growth retardation, race, gender, and maternal use of other drugs.

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In Other AMA Journals

ARCHIVES OF GENERAL PSYCHIATRY

On the Care of the Poor and the Uninsured

Boris M. Astrachan, MD, Donald J. Scherl, MD
(*Arch Gen Psychiatry.* 1991;48:481)

ARCHIVES OF DERMATOLOGY

The Dilemma of the Uninsured and Underinsured

Marvin Young, MD
(*Arch Dermatol.* 1991;127:712-713)

Radiological Case of the Month

David Ponder, MD; Gary S. Marshall, MD; Gerard P. Rabalais, MD (Contributors);
Beverly P. Wood, MD (Section Editor)

Patient 1.—A previously healthy 2-year-old girl presented with an intermittent low-grade fever, watery diarrhea, malaise, and decreased appetite of 6 weeks' duration. She lived in a rural community on a farm and had a pet dog. The parents confirmed a history of pica. Results of examination revealed a well-developed child with no abnormal physical findings. The lungs were clear on auscultation, the liver was not enlarged, and the optic fundi were normal.

Her white blood cell count was 42.4×10^9/L, with .05 band forms, .13 segmented neutrophils, .29 lymphocytes, .12 monocytes, and .41 eosinophils (the absolute eosinophil count was 17.4×10^9/L). The Westergren erythrocyte sedimentation rate was 87 mm/h, and results of stool examination for ova and parasites were negative. The serum IgG level was greater than 20 g/L, and isoagglutinin titers to A and B blood group antigens were normal. Figure 1 shows the patient's frontal chest radiograph.

Patient 2.—A 6-year-old boy presented with a cough, wheezing, fever, and intermittent abdominal pain of 3 months' duration. His family had emigrated from India several years earlier, and he had had a pet dog since arrival in this country. On physical examination, he was an active, well-developed boy with tachypnea, decreased breath sounds on auscultation of the chest, and diffuse expiratory wheezes. The liver was palpated 4 cm below the right costal margin. Results of the remainder of the examination were normal, including results of retinal examination. His white blood cell count was 57.6×10^9/L, with .06 band forms, .06 segmented neutrophils, .15 lymphocytes, .02 monocytes, and .71 eosinophils (the absolute eosinophil count was 40.9×10^9/L). The Westergren erythrocyte sedimentation rate was 108 mm/h, and results of stool examination for ova and parasites were negative. His serum IgG level was 40 g/L, and a serum isoagglutinin titer to blood group B antigen was 1:8192. Figure 2 shows his radiograph.

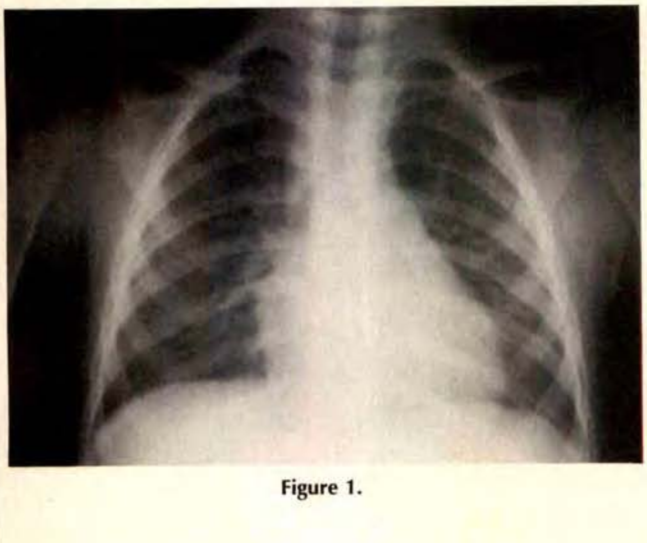

Figure 1.

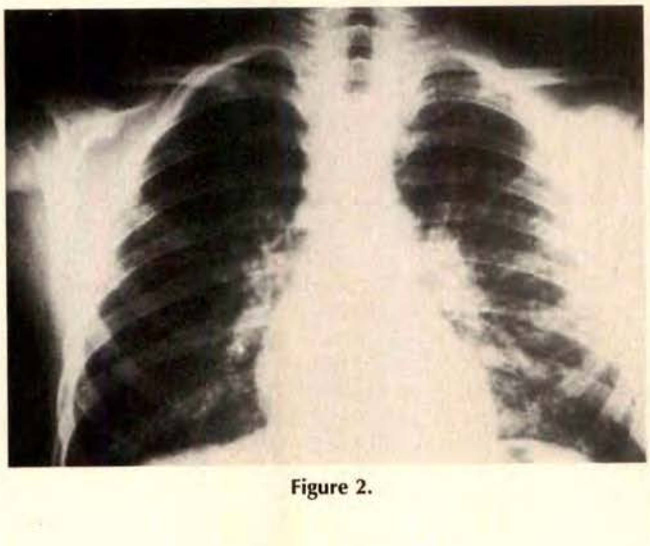

Figure 2.

Accepted for publication March 12, 1990.

From the Department of Pediatrics, University of Louisville (Ky) School of Medicine.

Reprint requests to the Department of Radiology, Childrens Hospital of Los Angeles, 4650 Sunset Blvd, Los Angeles, CA 90027 (Dr Wood).

Denouement and Discussion

Visceral Larva Migrans

Fig 1.—*Case 1. Both lungs have a mild, diffuse interstitial infiltrate. There is no pleural fluid, and the heart and mediastinal structures are normal.*

Fig 2.—*Case 2. Diffuse reticulonodular densities are evenly distributed bilaterally, with hilar adenopathy.*

Visceral larva migrans (VLM), first described in 1952,[1] is an infection of young children. It is characterized by fever, respiratory abnormalities, hepatomegaly, and marked eosinophilia. It is most commonly caused by infection with *Toxocara canis*, a dog ascarid. Infection occurs through ingestion of embryonated eggs in soil.[2] These eggs hatch second-stage larvae in the proximal small bowel that penetrate the intestinal wall and disseminate to the viscera, where they engender intense inflammatory reactions and may become encapsulated in eosinophilic granulomas. The clinical manifestations of VLM infection result from the mechanical effect of migrating larvae and from the vigorous immune response to them. Associated findings of leukocytosis, hypereosinophilia, and hypergammaglobulinemia, illustrated in these two patients, reflect the intensity of this host reaction.

Humans are accidental hosts in the life cycle of these helminths. As such, the helminths' maturation is arrested, and infected humans do not excrete infective eggs. In the most common form of transmission among dogs, puppies are infected in utero by migrating larvae. After birth, the larvae migrate through the lungs into the trachea, posterior pharynx, and gastrointestinal tract. There they mature into adults and shed eggs into the stool. The eggs require prolonged external incubation to become infective and can remain viable in soil for long periods, explaining the strong association between VLM and pica. Other risk factors for *T canis* infection include youth, being black, low levels of parental education, puppy ownership, and residence in the southeastern United States.[3]

These two cases illustrate the variety of manifestations of VLM infection. Fever, cough, wheezing, pallor, and abdominal discomfort are common complaints.[4] Infection can affect the central nervous system and cause seizures. Retinal involvement such as exudative granulomatous lesions is described in VLM-infected older children, who rarely manifest visceral disease. Hepatomegaly is the mos common physical finding; rashes and lymphadenopathy can also occur. Rales and/or rhonchi are sometimes present in patients with pulmonary symptoms of VLM infection.

The diagnosis of VLM infection is confirmed by the laboratory findings mentioned above and in elevated levels of isohemagglutinins, as demonstrated in patient 2. The latter results from cross-reactivity between blood group antigens and surface proteins of the parasite. Levels of hepatic transaminase are elevated, as illustrated in both patients. Roentgenographic abnormalities of the lung are evident and include diffuse or patchy alveolar infiltrates, miliary patterns, shifting infiltrates, and chronic interstitial changes.[5] The diagnosis can be confirmed by demonstrating larvae in a liver biopsy specimen or by detecting *Toxocara*-specific antibodies using enzyme-linked immunosorbent assay.[6] This test was performed in patient 1, and results were positive.

Infection with VLM is generally a self-limited condition, but treatment with antilarval chemotherapy or anti-inflammatory agents is indicated in patients experiencing compromised organ function.

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SPECIAL FEATURE

Picture of the Month

Merlin G. Butler, MD, PhD, Sarah Hassell, MD (Contributors); *Murray Feingold, MD* (Editor for This Case);
Walter W. Tunnessen, Jr, MD (Section Editor)

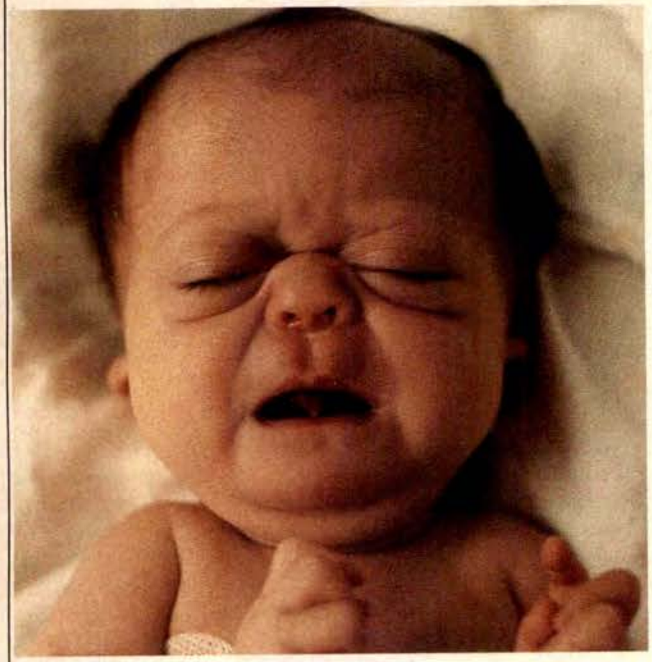
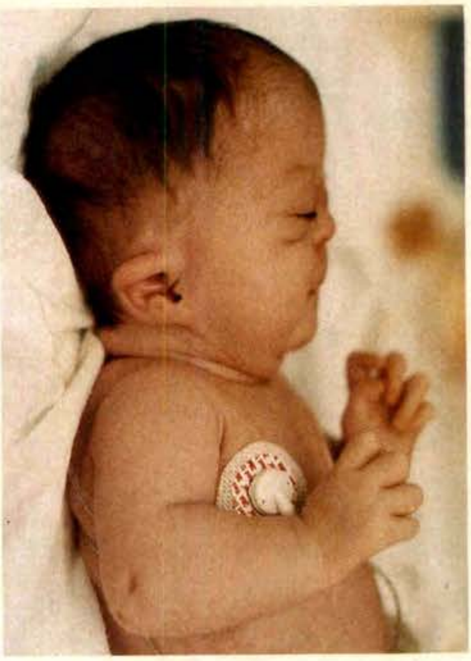


Figure 1.



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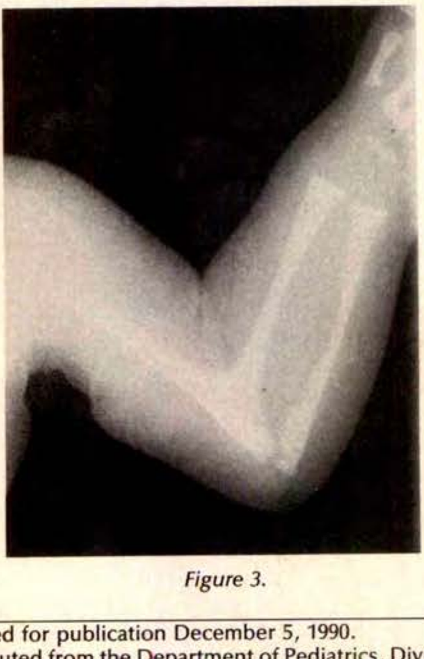

Figure 3.

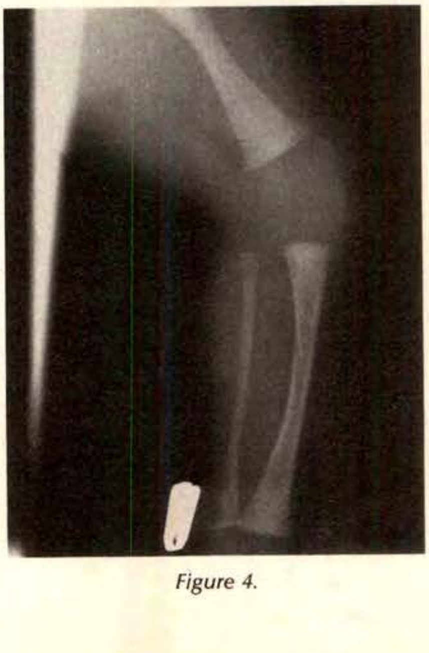

Figure 4.

Accepted for publication December 5, 1990.

Contributed from the Department of Pediatrics, Division of Genetics, Vanderbilt School of Medicine, Nashville, Tenn.

Reprint requests to National Birth Defects Center, Franciscan Children's Hospital, 30 Warren St, Brighton, MA 02135 (Dr Feingold).

Denouement and Discussion

Antley-Bixler Syndrome

Figs 1 and 2.—*3-week-old newborn with brachycephaly; prominent forehead; flat face; low-set, dysplastic ears; flattened nasal bridge; pear-shaped nose; severe, midface hypoplasia; proptosis; flexed position of elbow; and camptodactyly.*

Fig 3.—*Radiohumeral synostosis.*

Fig 4.—*Bowing of the femur.*

Manifestations

Major manifestations include craniosynostosis, a characteristic facial appearance, choanal atresia/stenosis, radiohumeral synostosis, bowing of femurs with fractures, and multiple joint contractures.

Craniofacial abnormalities consist of brachycephaly secondary to craniosynostosis of the coronal and lambdoidal sutures; large anterior fontanelle; and a face characterized by frontal bossing, flat facies, severe midface hypoplasia, proptosis, flattened nasal bridge, pear-shaped nose, choanal stenosis/atresia, long philtrum, and small, dysplastic ears.

Skeletal abnormalities include radiohumeral synostosis, anterior bowing of femurs with neonatal fractures, medial bowing of ulnas, narrow iliac wings, arachnodactyly with distal tapering of digits, camptodactyly, and scoliosis. Other occasional abnormalities are hydrocephalus, atrial septal defects, vaginal atresia, renal defects, multiple hemangiomata, and preauricular tags. Auditory dysfunction may also occur.

In most reported cases, prenatal and postnatal growth have been normal. Respiratory compromise generally occurs secondary to upper-airway obstruction (choanal stenosis/atresia occurs in about one half of affected individuals) and may vary from nasal congestion to apnea leading to death. Some patients have died in infancy of unexplained causes. Patients followed up beyond age 1 year have been ambulatory. Intelligence varies from normal to mild retardation.

Genetics

Antley-Bixler syndrome occurs sporadically, but has been reported in siblings and children of consanguineous parents. Therefore, inheritance is most likely autosomal recessive with a 25% recurrence risk for the condition in subsequent children from the same parents.

Treatment

Treatment consists of management of the orthopedic abnormalities, including the multiple joint contractures, through physical therapy, casting, and/or surgery. Surgery may also be necessary to alleviate upper-airway obstruction and to correct the craniosynostosis. Hearing, cardiac, and renal evaluations are also indicated. Genetic counseling and prenatal diagnosis should be discussed with the family.

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The Editors welcome contributions to Picture of the Month and Radiological Case of the Month. Those who wish to contribute should send their manuscripts to Dr Tunnessen (Picture of the Month*), The Children's Hospital of Philadelphia, 34th Street and Civic Center Blvd, Philadelphia, PA 19104, or Dr Wood* (Radiological Case of the Month*), Department of Radiology, Childrens Hospital of Los Angeles, 4650 Sunset Blvd, Los Angeles, CA 90027. Articles and photographs accepted for publication will bear the contributor's name. There is no charge for reproduction and printing of color illustrations.*

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References:
1. Walson PD et al. Ibuprofen, acetaminophen, and placebo treatment of febrile children. *Clin Pharmacol Ther.* 1989;46:9-17. 2. Data on file, McNeil Consumer Products Company.

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CLINICAL PHARMACOLOGY: Controlled clinical trials comparing doses of 5 and 10 mg/kg ibuprofen and 10-15 mg/kg of acetaminophen have been conducted in children 6 months to 12 years of age with fever primarily due to viral illnesses. In these studies there were no differences between treatments in fever reduction for the first hour and maximum fever reduction occurred between 2 and 4 hours. Response after 1 hour was dependent on both the level of temperature elevation as well as the treatment. In children with baseline temperatures at or below 102.5°F, both ibuprofen doses and acetaminophen were equally effective in their maximum effect. In those children with temperatures above 102.5°F, the ibuprofen 10 mg/kg dose was more effective. By 6 hours children treated with ibuprofen 5 mg/kg tended to have recurrence of fever, whereas children treated with ibuprofen 10 mg/kg still had significant fever reduction at 8 hours. In control groups treated with 10 mg/kg acetaminophen, fever reduction resembled that seen in children treated with 5 mg/kg of ibuprofen, with the exception that temperature elevation tended to return 1-2 hours earlier.

CONTRAINDICATIONS: PediaProfen should not be used in patients who have previously exhibited hypersensitivity to ibuprofen, or in individuals with all or part of the syndrome of nasal polyps, angioedema and bronchospastic reactivity to aspirin or other nonsteroidal anti-inflammatory agents. Anaphylactoid reactions have occurred in such patients.

WARNINGS: Risk of GI Ulceration, Bleeding and Perforation with NSAID Therapy. Serious gastrointestinal toxicity such as bleeding, ulceration, and perforation, can occur at any time, with or without warning symptoms, in patients treated chronically with NSAID therapy. Although minor upper gastrointestinal problems, such as dyspepsia, are common, usually developing early in therapy, physicians should remain alert for ulceration and bleeding in patients treated chronically with NSAIDs even in the absence of previous GI tract symptoms. In patients observed in clinical trials of several months to two years duration, symptomatic upper GI ulcers, gross bleeding or perforation appear to occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for one year. Physicians should inform patients about the signs and/or symptoms of serious GI toxicity and what steps to take if they occur.

Studies to date have not identified any subset of patients not at risk of developing peptic ulceration and bleeding. Except for a prior history of serious GI events and other risk factors known to be associated with peptic ulcer disease, such as alcoholism, smoking, etc., no risk factors (e.g., age, sex) have been associated with increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less well than other individuals and most spontaneous reports of fatal GI events are in this population. Studies to date are inconclusive concerning the relative risk of various NSAIDs in causing such reactions. High doses of any NSAID probably carry a greater risk of these reactions, although controlled clinical trials showing this do not exist in most cases. In considering the use of relatively large doses (within the recommended dosage range), sufficient benefit should be anticipated to offset the potential increased risk of GI toxicity.

PRECAUTIONS: General: Blurred and/or diminished vision, scotomata, and/or changes in color vision have been reported. If a patient develops such complaints while receiving **PediaProfen**, the drug should be discontinued and the patient should have an ophthalmologic examination which includes central visual fields and color vision testing.

Fluid retention and edema have been reported in association with ibuprofen; therefore, the drug should be used with caution in patients with a history of cardiac decompensation or hypertension.

PediaProfen, like other nonsteroidal anti-inflammatory agents, can inhibit platelet aggregation, but the effect is quantitatively less and of shorter duration than that seen with aspirin. Ibuprofen has been shown to prolong bleeding time (but within the normal range) in normal subjects. Because this prolonged bleeding effect may be exaggerated in patients with underlying hemostatic defects, **PediaProfen** should be used with caution in persons with intrinsic coagulation defects and those on anticoagulant therapy.

Patients on **PediaProfen** should report to their physicians signs or symptoms of gastrointestinal ulceration or bleeding, blurred vision or other eye symptoms, skin rash, weight gain, or edema.

In order to avoid exacerbation of disease of adrenal insufficiency, patients who have been on prolonged corticosteroid therapy should have their therapy tapered slowly rather than discontinued abruptly when ibuprofen is added to the treatment program.

The antipyretic and anti-inflammatory activity of **PediaProfen** may reduce fever and inflammation, thus diminishing their utility as diagnostic signs in detecting complications of presumed noninfectious, noninflammatory painful conditions.

Since ibuprofen is eliminated primarily by the kidney, patients with significantly impaired renal function should be closely monitored and a reduction in dosage should be anticipated to avoid drug accumulation. Prospective studies on the safety of ibuprofen in patients with chronic renal failure have not been conducted.

Safety and efficacy of **PediaProfen** in children below the age of 6 months has not been established.

Pregnancy: Reproductive studies conducted in rats and rabbits at doses somewhat less than the maximal clinical dose did not demonstrate evidence of developmental abnormalities. However, animal reproduction studies are not always predictive of human response. As there are no adequate and well-controlled studies in pregnant women, this drug should be used during pregnancy only if clearly needed. Because of the known effects of nonsteroidal anti-inflammatory drugs on the fetal cardiovascular system (closure of ductus arteriosus), use during late pregnancy should be avoided. As with other drugs known to inhibit prostaglandin synthesis, an increased incidence of dystocia and delayed parturition occurred in rats. Administration of **PediaProfen** is not recommended during pregnancy.

ADVERSE REACTIONS: The most frequent type of adverse reaction occurring with ibuprofen is gastrointestinal. In controlled clinical trials, the percentage of adult patients reporting one or more gastrointestinal complaints ranged from 4% to 16%.

Adverse reactions occurring in 3% to 9% of patients treated with ibuprofen: nausea, epigastric pain, heartburn, dizziness, rash. *Adverse reactions occurring in 1% to 3% of patients:* diarrhea, abdominal distress, nausea and vomiting, indigestion, constipation, abdominal cramps or pain, fullness of GI tract, headache, nervousness, pruritus, tinnitus, decreased appetite, edema, fluid retention (generally responds promptly to drug discontinuation). Still other reactions (less than 1 in 100) have been reported, and are detailed in the full summary of prescribing information.

DOSAGE AND ADMINISTRATION: Shake well prior to administration.

Fever Reduction in Children 6 months to 12 years of age: Dosage should be adjusted on the basis of the initial temperature level (See CLINICAL PHARMACOLOGY for a description of the controlled clinical trial results). The recommended dose is 5 mg/kg if the baseline temperature is less than 102.5°F or 10 mg/kg if the baseline temperature is greater than 102.5°F. The duration of fever reduction is generally 6-8 hours and is longer with the higher dose. The recommended maximum daily dose is 40 mg/kg.

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References: 1. Sandler RB, et al: *Am J Clin Nutr* 1985;42:270-274. 2. Rubin K: *Pediatric By-Line* 1985;4(3):1, 4-6. 3. Marston R, Raper N: *National Food Review* 1987;36:18-23. 4. Heaney RH: *The Physician and Sportsmedicine* 1987;15:83-88.

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NEONATOLOGIST to join five-member BC/BE group in a Level III perinatal center with academic affiliation. For further information, contact: B.T. Bloom, MD, 550 North Hillside, Wichita, KS 67214. (316) 688-2360.

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THIRD PEDIATRICIAN – BRAINERD, MINNESOTA: Join two pediatricians of 22 multi-specialty clinic. No set-up cost. Two hours from Minneapolis. Beautiful lakes and trees; ideal for families. Call collect/write: Curt Nielsen, (218) 828-7105 or (218) 829-4901; Brainerd Medical Center, P.O. Box 524, Brainerd, MN 56401.

FOUR CONGENIAL PEDIATRICIANS seek fifth pediatrician for rapidly expanding practice. This practice is located in an affluent growing community in northern California within a two-hour access to San Francisco and Lake Tahoe. Guaranteed salary for two years with partnership options at the end of the two-year period. Write or call: P.O. Box 787, Lodi, CA 95240. (209) 369-7493.

PEDIATRICIAN: Lovely agricultural, family oriented community located in western Nebraska (3 hours from Denver and Rocky Mountain snow activities) is seeking a fourth pediatrician. Choose from partnership, solo or salaried positions. Practice at the 270-bed regional referral center. Receive a first year's income of $80,000 plus an attractive benefits package. This area has outstanding recreational activities and highly rated schools. Call Lori at (800) 328-3666, or send CV to: Physician Source, 95 Cedar Lane, Englewood, NJ 07631.

PLEASE NOTE – Address replies to box number ads as follows: Box number ________, c/o AJDC, P.O. Box 1510, Clearwater, FL 34617.

Professional Opportunities

PHILADELPHIA – Children's Hospital of Philadelphia seeks BC/BE pediatricians for its general pediatric practices. Exciting opportunity to practice in an academic setting. Responsibilities include ambulatory patient care and clinical teaching (affiliated with UPenn Medical School). Opportunities for clinical research and in-patient supervision. Competitive salary and excellent fringe benefits. Send CV to: Frances M. Gill, MD, Suite 2013, General Pediatrics, 1 Children's Plaza, Philadelphia, PA 19104. Children's Hospital of Philadelphia is an equal opportunity/affirmative action employer.

PROVIDENCE, RHODE ISLAND: Pediatrician to join seven others in well-run network of community health centers, serving multi-ethnic population. Involvement in Brown University's Medical School teaching program encouraged. Start any time between now and September. Call/write: Stanley Block, MD, Providence Ambulatory Health Care Foundation, 469 Angell Street, Providence, RI 02906. (401) 861-6300. An AA/EEE.

ADIRONDACK FOOTHILLS opportunity! Modern 124-bed hospital in upstate New York is offering a generous financial package for BC/BE pediatrician interested in establishing a private practice with excellent coverage arrangements. Guaranteed income, start-up funds, malpractice insurance, cash-flow assistance. Located in a family-oriented community with year-round recreation, excellent schools, and beautiful surroundings. Contact: Lyn I. Kucij, Director of Marketing and Development, Nathan Littauer Hospital, 99 East State Street, Gloversville, NY 12078. (518) 773-5504. Please call collect.

IMMEDIATE OPENING for BC/BE pediatrician to associate with well-established, rapidly growing, 32-MD multi-specialty group. Located in the San Francisco Bay area in a growing community serving 170,000. Patients include both fee-for-service and prepaid health plan. Attractive compensation and benefits. Malpractice provided. California license required. Send CV to: Bart Bona, Administrator, Fairfield Medical Group, Caller Box 4020, Fairfield, CA 94533-0410. (707) 426-3911.

DELAWARE – General Pediatrician: The Nemours Foundation will develop several new general pediatric clinics in southern Delaware. These privately funded and administered clinics will offer a unique opportunity to serve a growing pediatric population in a coordinated statewide health care system. They will be located in underserved semi-rural areas and will consist of a general pediatrician and a pediatric nurse practitioner working together as a team in a modern computerized office setting. Tertiary care will be provided by the Alfred I. duPont Institute in Wilmington, Delaware. These clinics will be minutes from the Atlantic beaches and the Chesapeake Bay. The major metropolitan areas of Washington, Baltimore, Philadelphia and Wilmington will be within a two hour drive. If you have a desire to serve children in genuine need of good medical care, reply to the address below. Salary and fringes are distinctly above average. Reply to: The Alfred I. duPont Institute, Thomas P. Ferry, Administrator, P.O. Box 269, Wilmington, DE 19899. Telephone: (302) 651-4000.

MAINE: Immediate opportunity for a fourth BC/BE pediatrician with general and/or subspecialty interests to join a multi-specialty group affiliated with a 250-bed regional referral hospital. Enjoy the professional challenge offered in a sophisticated medical community along with the wonderful recreational opportunities and quality of life in Maine. Please send CV to: Richard Marsh, MD, 76 High Street, Suite 203, Lewiston, ME 04240. Or call: (207) 795-2389 and ask for Shannon Tamminen.

Professional Opportunities

TWO PEDIATRICIANS seeking third BC/BE pediatrician to join two site, growing practice. Ideal all season recreational area. Ideal site for young family. Please contact: Tahoe City Pediatrics, P.O. Box 6959, Tahoe City, CA 95730.

ROCHESTER, NEW YORK – Opportunity for a general pediatrician to develop their practice as part of the Rochester Medical Group pediatric department. Rochester Medical Group is a multi-specialty group practice which cares for fee-for-service as well as prepaid patients. In addition to full-time position, willing to consider part-time or job-share opportunities. Subspecialty interests possible. University affiliation encouraged. Competitive salary and benefits. Located in attractive metropolitan area with many cultural and recreational advantages. Send resume or call: Rochester Medical Group, P.C. Attention: James Tobin, MD, 800 Carter Street, Rochester, NY 14621. (716) 338-1400. EOE, M/F.

NEONATOLOGIST: Marshfield Clinic, a 350 physician multi-specialty private group practice in central Wisconsin, is seeking a fourth BC/BE neonatologist to join its 20-member pediatric department. Adjacent 524-bed acute care teaching hospital includes a 24-bed, Level III Neonatal Unit. Full pediatric support subspecialties are available on-site. Pediatric Residency Program, University of Wisconsin Medical School affiliation, Medical Research Foundation and large regional referral base contribute to a very stimulating environment. Marshfield, a community of 20,000, was recently designated as "one of the best small cities in the Midwest." Send curriculum vitae plus the names of several references to: James C. Opitz, MD, Marshfield Clinic, 1000 North Oak Avenue, Marshfield, WI 54449. Or call collect: (715) 387-5016.

UPSTATE NEW YORK – BC/BE pediatrician to join well established pediatric group. Early partnership. Nice, safe community. Call or CV to: Felipe Canizares, MD, 421 Main Street, Oneida, NY 13421. (315) 363-2350.

NORTHWESTERN PENNSYLVANIA – BC pediatrician seeks second pediatrician (BC/BE) to be on team of well-established, quality care multi-specialty group of eighteen physicians in town of 15,000. Exceptional hospital with 12-bed pediatric unit and Level I nursery serving 600 deliveries a year. Excellent living and working environment. Attractive salary and benefits. Send CV: Box #121, c/o AJDC.

OPPORTUNITY FOR EXCELLENT practice in high desert area of New Mexico. Our southwest paradise cares about its children and their physicians. Call coverage and financial assistance available. Call Jo Grimm, (800) 638-6942.

UPSTATE NEW YORK – BC/BE pediatrician wanted to join two pediatricians in semi-rural Columbia County. Part-time now. Full-time in 1-3 years. 2½ hours to New York City or Boston. ½ hour to skiing or Tanglewood. An opportunity for someone interested in practicing good pediatrics and enjoying living. Send CV to: Ira Marks, MD, Chatham, NY 12037.

PEDIATRICIAN – Autauga Medical Center, Prattville, Alabama. Well-established community hospital wishes to add pediatrician to its staff. Affluent community fifteen minutes from Montgomery, Alabama. Excellent call coverage, superior salary/compensation package offered. Please call Kevin McGrane at (800) 776-5776 for more details.

WASHINGTON – Established, five full-time, one part-time pediatric group seeking full-time BC/BE pediatrician. Beautiful, rapidly growing community in midst of mountains and water, one hour from Seattle. Local hospital and nearby childrens' hospitals. Opportunity to practice a wide range of pediatric skills. Competitive salary; early partnership. Reply with cover letter and CV to: Medical Director, Kitsap Children's Clinic, 2625 Wheaton Way, Suite A, Bremerton, WA 98310. (206) 479-1651.

PLEASE NOTE – Address replies to box number ads as follows: Box number ________ , c/o AJDC, P.O. Box 1510, Clearwater, FL 34617.

SPECIALIST – PEDIATRICS

Western Regional Health Centre

Due to growing demand, the Western Regional Health Centre, located in Yarmouth, Nova Scotia, requires the services of a second person in the specialty of pediatrics.

The Centre which services a population of 60,000 consists of a fully accredited regional hospital (188 beds), an adult residential centre, a nursing home, and a RN School of Nursing. The hospital is fully equipped with readily available support services including ultra sound and 24 hour laboratory coverage and has on-site office rental space available. Family physicians provide 24 hour on-site coverage of the ER/OPD Department.

Yarmouth, is a seaport town located in southwestern Nova Scotia that offers an attractive life style. It is only a three-hour drive to Halifax and there are convenient transportation services, including air and automobile ferries to larger centres in Canada and New England, U.S.A.

Income will be based on fee-for-service in an area with a limited number of specialists and proven need of the population.

Applications should be Canadian board-eligible with LMCC, National Boards or FLEX.

Interested applicants are requested to apply by writing to:

Mr. J.G. McEachern
Executive Director
Western Regional Health Centre
60 Vancouver Street, Yarmouth, Nova Scotia B5A 2P5

Pediatric Subspecialists

Cardiology
Pulmonology
Hematology/Oncology
Neurology
Surgery
Neonatology

The University of South Dakota School of Medicine currently has openings for BE/BC pediatric subspecialties.

These are full-time academic positions ideally suited for the clinician scholar who wishes to develop and guide a program which will have a significant impact on the health care of children. Although our program is heavily slanted toward medical student education and patient care, the department encourages and provides ample resources for clinical and laboratory research.

Sioux Falls, included in David Frankes' book, America's Fifty Safest Cities, has a strong economic base, growing population and a progressive educational system. South Dakota's four season climate welcomes endless recreational activities year-round.

Competitive financial packages offered. EOE/AAE.

Send CV or call:
Carl Hinson • (800) 468-3333

USD School of Medicine
1100 South Euclid, P.O. Box 5039
Sioux Falls, SD 57117

Professional Opportunities

IDAHO – Multi-specialty group of 27 physicians needs fourth pediatrician. Guaranteed salary plus bonus first year. Full stockholder status thereafter. Many fringe benefits and excellent outdoor recreational activities in agricultural area twenty miles from state capital. Office adjacent to 165-bed hospital with Level II nursery. Contact: Mike Crane, 215 East Hawaii Avenue, Nampa, ID 83686. (208) 467-1121.

CALIFORNIA – Multi-specialty private group practice located in desirable high growth area of southern California seeks general pediatricians, as well as pediatricians with subspecialty of infectious disease, neurology or cardiology. Excellent working conditions, fringe benefits, and congenial staff. Please submit CV to: George Kanaly, PhD, President, Riverside Medical Clinic, 3660 Arlington Avenue, Riverside, CA 92506.

Faculty Positions

AMBULATORY PEDIATRICS Non specified – The Department of Pediatrics, University of Illinois College of Medicine at Rockford seeks a BC/BE pediatrician for an academic position in an ambulatory setting. The Community Health Center program is a longitudinal, comprehensive experience in primary care medicine. Each center is staffed by full-time faculty. Responsibilities include supervision of medical students in an ambulatory setting, direct patient care, quality assurance activities and clinical research. For earliest consideration please reply by: May 1, 1991. Reply with CV to: D.H. Wortmann, MD, Chairman, Department of Pediatrics, UICOM-R, 1400 Charles Street, Rockford, IL 61104. UICOM-R is an equal opportunity/affirmative action employer.

Fellowships

Fellowship
Child Abuse and Neglect Prevention Program
Medical College of Ohio

The Department of Pediatrics at the Medical College of Ohio in Toledo is seeking a BC/BE pediatrician for a two-year fellowship in the Child and Family Assessment Unit.

Applicant must be interested in the developmental and psychosocial aspects of pediatrics care as they relate to child abuse and neglect. Familiarity with the use of the colposcope desirable, but not essential. Ability to function in a multidisciplinary team setting necessary. Salary is $30,000 a year.

Inquiries should be directed to Brenda Ballmer, Department of Pediatrics, Medical College of Ohio, P.O. Box 10008, Toledo, Ohio 43699-0008, (419) 381-4485.

The Medical College of Ohio is an affirmative action/equal opportunity employer.

PLEASE NOTE – Address replies to box number ads as follows: Box number ________ , c/o AJDC, P.O. Box 1510, Clearwater, FL 34617.

Faculty Positions

SOUTHEAST USA – Academic pediatrician: Teach medical students and family practice residents. Direct patient care and clinical research interests required. Alabama state medical license required. Should be board-eligible or board-certified. The University of Alabama is an equal opportunity affirmative action employer. Send inquiries with CV to: David C. Hefelfinger, MD, Department of Pediatrics, 700 University Boulevard East, Tuscaloosa, AL 35401. (205) 348-1304.

PEDIATRICIAN – Seeking BC/BE MD or DO pediatrician for full-time faculty position with clinical and academic responsibilities. Send CV to: Lawrence E. Jacobson, DO, Dean for Academic Affairs, University of Osteopathic Medicine and Health Sciences, 3200 Grand Avenue, Des Moines, IA 50312.

JUNIOR FACULTY POSITION in the Division of General/Ambulatory Pediatrics is available at Texas Tech University Health Sciences Center, School of Medicine, Lubbock, Texas. Applicant must be board-eligible/-certified. Responsibilities include teaching, patient care and clinical research. Tenure track appointment available to qualified candidates. Call or submit CV to: V.J. Gururaj, MD, Professor, Director Division General/Ambulatory Pediatrics, Texas Tech University Health Sciences Center, School of Medicine, Department of Pediatrics, Lubbock, TX 79430. (806) 743-2266.

Faculty Positions

WYOMING – University of Wyoming Famil
Residency-Casper is seeking an experien
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pediatric coordinator of an 8-8-8 family pra
dency program. Level II Nursery skills ar
60% teaching, 20% direct patient ca
research. This is a tenure track position.
approval will be required prior to filling this
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BC/BE PEDIATRIC CARDIOLOGIST nee
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Send CV to: Drs. Joon Park or
Sridaromont, Pediatrics, Texas Tech U
Health Sciences Center, Lubbock, TX 794
743-3088. TTUHSC is an equal opportunit
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Positions Available

FLORIDA – Energetic, BC/BE pediatricia
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NW 70th Avenue, Suite 350A, Plantation, F
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DISEASES OF CHILDREN
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Classified Department, P.O. Box 1510, Clearwater, Florida 34617
National (800) 237-9851 ◆ Local (813) 443-7666

Yesterday, she was infested with lice.

Today, she's back in school.

Nothing gets kids back to class faster than A-200.

When a child gets lice, most schools have a No Nit Policy to prevent reinfestation nd epidemics. This means if a parent doesn't use a pediculicide therapy system hat's 100% effective at both killing and removing lice and nits, a child could be denied eadmission to school and miss some important learning. That's why you should ecommend the clinically proven efficacy of Advanced Formula A-200.

The A-200 Lice Treatment System can have a child louse-free, nit-free and ack in school the next day. A-200 Shampoo has been shown to be 100% ffective at killing lice,* and the patented A-200 Nit Comb is proven capable of emoving all nits from the hair,* to meet the requirements of the No Nit Policy.

The active ingredients in A-200 are piperonyl butoxide and natural yrethrins; it's gentle on hair and scalp, yet fatal to lice.

So the next time lice invade your practice, recommend A-200. ecause nothing gets kids back to class faster.

A-200 takes the life out of lice.

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56

AMERICAN JOURNAL OF
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NOVEMBER 1991

v cm

Vertical Transmission of Human Immunodeficiency Virus From Seronegative or Indeterminate Mothers
J. P. Johnson, P. E. Vink, S. E. Hines, B. Robinson, J. C. Davis, Jr, P. Nair

Commotio Cordis: The Single, Most Common Cause of Traumatic Death in Youth Baseball
T. J. Abrunzo

Prevalence of Birth Defects Among Low-Birth-Weight Infants: A Population Study
F. Mili, L. D. Edmonds, M. J. Khoury, A. B. McClearn

Pediatric Germ Cell and Human Chorionic Gonadotropin–Producing Tumors: Clinical and Laboratory Features
A. T. Englund, M. E. Geffner, R. A. Nagel, B. M. Lippe, G. D. Braunstein

Acellular Pertussis Vaccines: Efficacy and Evaluation of Clinical Case Definitions
W. C. Blackwelder, J. Storsaeter, P. Olin, H. O. Hallander

Volume 145, Number 11

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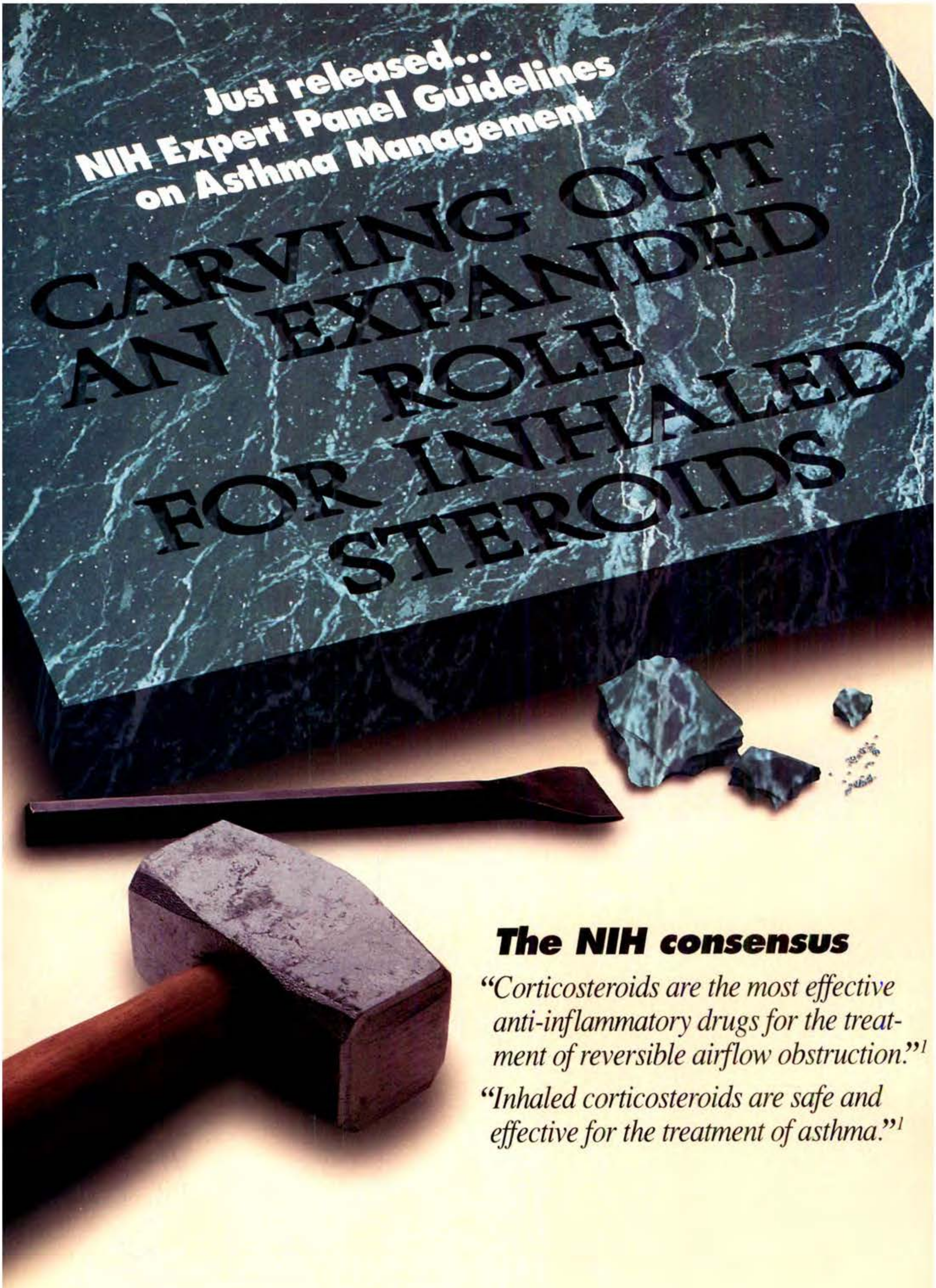

The NIH consensus

"Corticosteroids are the most effective anti-inflammatory drugs for the treatment of reversible airflow obstruction."[1]

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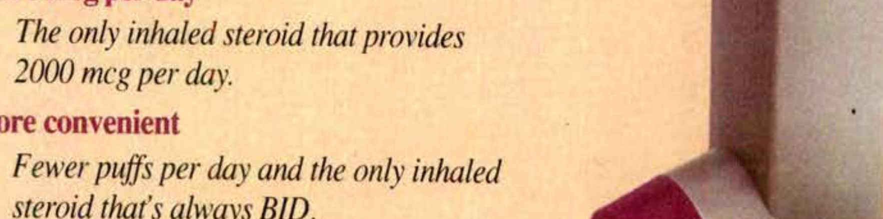

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  The only inhaled steroid that provides 2000 mcg per day.

- **More convenient**

  Fewer puffs per day and the only inhaled steroid that's always BID.

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St. Louis, Missouri 63043-9979

Please see accompanying brief summary which follows.

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AeroBid® (flunisolide)

Effective asthma control BID

For oral inhalation only

CONTRAINDICATIONS

AeroBid Inhaler is contraindicated in the primary treatment of status asthmaticus or other acute episodes of asthma where intensive measures are required.

Hypersensitivity to any of the ingredients of this preparation contraindicates its use.

WARNINGS

Particular care is needed in patients who are transferred from systemically active corticosteroids to AeroBid Inhaler because deaths due to adrenal insufficiency have occurred in asthmatic patients during and after transfer from systemic corticosteroids to aerosol corticosteroids. After withdrawal from systemic corticosteroids, a number of months are required for recovery of hypothalamic-pituitary-adrenal (HPA) function. During this period of HPA suppression, patients may exhibit signs and symptoms of adrenal insufficiency when exposed to trauma, surgery or infections, particularly gastroenteritis. Although AeroBid Inhaler may provide control of asthmatic symptoms during these episodes, it does NOT provide the systemic steroid that is necessary for coping with these emergencies.

During periods of stress or a severe asthmatic attack, patients who have been withdrawn from systemic corticosteroids should be instructed to resume systemic steroids (in large doses) immediately and to contact their physician for further instruction. These patients should also be instructed to carry a warning card indicating that they may need supplementary systemic steroids during periods of stress or severe asthma attack. To assess the risk of adrenal insufficiency in emergency situations, routine tests of adrenal cortical function, including measurement of early morning resting cortisol levels, should be performed periodically in all patients. An early morning resting cortisol level may be accepted as normal if it falls at or near the normal mean level.

Localized infections with Candida albicans or Aspergillus niger have occurred in the mouth and pharynx and occasionally in the larynx. Positive cultures for oral Candida may be present in up to 34% of patients. Although the frequency of clinically apparent infection is considerably lower, these infections may require treatment with appropriate antifungal therapy or discontinuance with AeroBid Inhaler.

AeroBid Inhaler is not to be regarded as a bronchodilator and is not indicated for rapid relief of bronchospasm.

Patients should be instructed to contact their physician immediately when episodes of asthma that are not responsive to bronchodilators occur during the course of treatment. During such episodes, patients may require therapy with systemic corticosteroids.

There is no evidence that control of asthma can be achieved by administration of the drug in amounts greater than the recommended doses, which appear to be the therapeutic equivalent of approximately 10 mg/day of oral prednisone. Theoretically, the use of inhaled corticosteroids with alternate day prednisone systemic treatment should be accompanied by more HPA suppression than a therapeutically equivalent regimen of either alone.

Transfer of patients from systemic steroid therapy to AeroBid Inhaler may unmask allergic conditions previously suppressed by the systemic steroid therapy, e.g., rhinitis, conjunctivitis, and eczema.

PRECAUTIONS

General: Because of the relatively high molar dose of flunisolide per activation in this preparation, and because of the evidence suggesting higher levels of systemic absorption with flunisolide than with other comparable inhaled corticosteroids, patients treated with AeroBid should be observed carefully for any evidence of systemic corticosteroid effect, including suppression of bone growth in children. Particular care should be taken in observing patients post-operatively or during periods of stress for evidence of a decrease in adrenal function. During withdrawal from oral steroids, some patients may experience symptoms of systemically active steroid withdrawal, e.g., joint and/or muscular pain, lassitude and depression, despite maintenance or even improvement of respiratory function.

In responsive patients, flunisolide may permit control of asthmatic symptoms without suppression of HPA function. Since flunisolide is absorbed into the circulation and can be systemically active, the beneficial effects of AeroBid Inhaler in minimizing or preventing HPA dysfunction may be expected only when recommended dosages are not exceeded.

The long-term effects of the drug in human subjects are still unknown. In particular, the local effects of the agent on developmental or immunologic processes in the mouth, pharynx, trachea, and lung are unknown. There is also no information about the possible long-term systemic effects of the agent.

The potential effects of the drug on acute, recurrent, or chronic pulmonary infections, including active or quiescent tuberculosis, are not known. Similarly, the potential effects of long-term administration of the drug on lung or other tissues are unknown.

Pulmonary infiltrates with eosinophilia may occur in patients on AeroBid Inhaler therapy. Although it is possible that in some patients this state may become manifest because of systemic steroid withdrawal when inhalational steroids are administered, a causative role for the drug and/or its vehicle cannot be ruled out.

Carcinogenesis: A 22-month study was conducted in Swiss derived mice to evaluate the carcinogenic potential of the drug. There was an increase in the incidence of pulmonary adenomas within the range of adenomas previously reported in the literature for untreated or control Swiss derived mice. An additional study is being conducted in a species with a lower incidence of spontaneous pulmonary tumors.

Impairment of fertility: Female rats receiving high doses of flunisolide (200 mcg/kg/day) showed some evidence of impaired fertility. Reproductive performance in the low (8 mcg/kg/day) and mid-dose (40 mcg/kg/day) groups was comparable to controls.

Pregnancy: Pregnancy Category C. As with other corticosteroids, flunisolide has been shown to be teratogenic in rabbits and rats at doses of 40 and 200 mcg/kg/day respectively. It was also fetotoxic in these animal reproductive studies. There are no adequate and well-controlled studies in pregnant women. Flunisolide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because other corticosteroids are excreted in human milk, caution should be exercised when flunisolide is administered to nursing women.

ADVERSE REACTIONS

Adverse events reported in controlled clinical trials and long-term open studies in 514 patients treated with AeroBid are described below. Of those patients, 463 were treated for 3 months or longer, 407 for 6 months or longer, 287 for 1 year or longer, and 122 for 2 years or longer.

Musculoskeletal reactions were reported in 35% of steroid-dependent patients in whom the dose of oral steroid was being tapered. This is a well-known effect of steroid withdrawal.

Incidence 10% or greater

Gastrointestinal: diarrhea (10%), nausea and/or vomiting (25%), upset stomach (10%); *General:* flu (10%); *Mouth and Throat:* sore throat (20%); *Nervous System:* headache (25%); *Respiratory:* cold symptoms (15%), nasal congestion (15%), upper respiratory infection (25%); *Special Senses:* unpleasant taste (10%).

Incidence 3-9%

Cardiovascular: palpitations; *Gastrointestinal:* abdominal pain, heartburn; *General:* chest pain, decreased appetite, edema, fever; *Mouth and Throat:* Candida infection; *Nervous System:* dizziness, irritability, nervousness, shakiness; *Reproductive:* menstrual disturbances; *Respiratory:* chest congestion, cough,* hoarseness, rhinitis, runny nose, sinus congestion, sinus drainage, sinus infection, sinusitis, sneezing, sputum, wheezing*; *Skin:* eczema, itching (pruritus), rash; *Special Senses:* ear infection, loss of smell or taste.

Incidence 1-3%

General: chills, increased appetite and weight gain, malaise, peripheral edema, sweating, weakness; *Cardiovascular:* hypertension, tachycardia; *Gastrointestinal:* constipation, dyspepsia, gas; *Hemic/Lymph:* capillary fragility, enlarged lymph nodes; *Mouth and Throat:* dry throat, glossitis, mouth irritation, pharyngitis, phlegm, throat irritation; *Nervous System:* anxiety, depression, faintness, fatigue, hyperactivity, hypoactivity, insomnia, moodiness, numbness, vertigo; *Respiratory:* bronchitis, chest tightness,* dyspnea, epistaxis, head stuffiness, laryngitis, nasal irritation, pleurisy, pneumonia, sinus discomfort; *Skin:* acne, hives, or urticaria; *Special Senses:* blurred vision, earache, eye discomfort, eye infection.

Incidences less than 1%, judged by investigators as possibly or probably drug-related: abdominal fullness, shortness of breath.

*The incidences as shown of cough, wheezing, and chest tightness were judged by investigators to be possibly or probably drug-related. In placebo-controlled trials, the overall incidences of these adverse events (regardless of investigators' judgement of drug relationship) were similar for drug and placebo-treated groups. They may be related to the vehicle or delivery system.

CAUTION: Federal law prohibits dispensing without prescription.
For full prescribing information, please see package insert.

(NDC 0456-0672-99)

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References:

1. *National Heart, Lung, and Blood Institute National Asthma Education Program Expert Panel Report—Guidelines for the Diagnosis and Management of Asthma.* Bethesda, Md: US Dept of Health and Human Services; 1991.
2. *Physicians' Desk Reference®.* 45th ed. Oradell, NJ: Medical Economics Co Inc; 1991:955, 1862, 2026.

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INDEX TO ADVERTISERS

Burroughs Wellcome Company .... Cover 3

Child Health 1260

Drug Free America 1332

Fisons Corporation 1216, 1283-1284
Forest Pharmaceuticals .... Cover 2-1214

ICN Pharmaceuticals 1221-1222

McNeil Consumer Products Company ... 1228A-B, 1303-1304
Merck Sharp & Dohme
Division of Merck & Co., Inc. 1277-1278

National Dairy Board 1259

Procter & Gamble 1218

Richardson-Vicks 1298
A. H. Robins Company .... Cover 4
Rorer Pharmaceuticals 1252-1254

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AMERICAN JOURNAL OF DISEASES OF CHILDREN

AJDC

Vol 145 **No. 11** **NOVEMBER 1991**

THE PEDIATRIC FORUM

Call for Abstracts 1223

Sudden Cardiac Death 1223
William Pearl, MD, El Paso, Tex

***Staphylococcus aureus* in Impetigo** 1223
Ron Dagan, MD, Beer-Sheva, Israel

In Reply 1223
James W. Bass, MD, Honolulu, Hawaii

Treatment Withdrawal in Neonates 1223
Paul Byrne, MB, CHB, FRCPC,
R. Welch, MB, CHB, MRCP, Edmonton, Canada

Exacerbation of Tinea Corporis During Treatment With 1% Clotrimazole/0.05% Betamethasone Diproprionate (Lotrisone) 1224
Ronald D. Reynolds, MD, New Richmond, Ohio;
Susan Boiko, MD, Anne W. Lucky, MD, Cincinnati, Ohio

Mediterranean Visceral Leishmaniasis: A Frequently Unrecognized Imported Disease 1225
Ludo M. Mahieu, MD, Karel J. Van Acker, MD, PhD, Antwerpen, Belgium

Send Linus to Me 1227
Harriet Szonyi, Toronto, Ontario

In Reply 1227
Patrick C. Friman, PhD, Philadelphia, Pa

A Markedly Immature Lecithin-Sphingomyelin Ratio at Term and Congenital Hypothyroidism 1227
Gary R. Cohen, MD; James Thorp, MD; John D. Yeast, MD;
Bruce A. Meyer, MD; Richard O'Kell, MD;
Candace Macy, Kansas City, Mo

EDITORIAL

Is Prophylaxis of Neonates With Intravenous Immunoglobulin Beneficial? 1229
Harvy R. Hill, MD, Salt Lake City, Utah

ARTICLES

Efficacy and Pharmacokinetics of Intravenous Immune Globulin Administration to High-Risk Neonates 1233
Janet Kinney, MD; Lucinda Mundorf, RN; Christine Gleason, MD;
Carlton Lee, PharmD; Timothy Townsend, MD; Roshelle Thibault, RPh;
Anna Nussbaum, MD; Helen Abby, PhD; Robert Yolken, MD, Baltimore, Md

Continued on page 1217.

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AMERICAN JOURNAL OF DISEASES OF CHILDREN

Vertical Transmission of Human Immunodeficiency Virus From Seronegative or Indeterminate Mothers 1239
John P. Johnson, MD; Peter E. Vink, MD; Susan E. Hines, MS, C PNP;
Barbara Robinson, RNC; John C. Davis, Jr, MD;
Prasanna Nair, MD, Baltimore, Md

Child Survival and Perinatal Infections With Human Immunodeficiency Virus 1242
John V. Bennett, MD, Martha F. Rogers, MD, Atlanta, Ga

Clinical and Endocrinologic Manifestations in Perinatally Human Immunodeficiency Virus Type 1–Infected Children Aged 5 Years or Older 1248
Philippe Lepage, MD; Philippe Van de Perre, MD;
Guy Van Vliet, MD, PhD; François Nsengumuremyi, MD;
Christiaan Van Goethem, MD; Philippe Kestelyn, MD, Brussels, Belgium;
Philippe Msellati, MD, Bordeaux, France;
Deo-Gratias Hitimana, MD, Brussels, Belgium

Obesity Among Mescalero Preschool Children: Association With Maternal Obesity and Birth Weight 1262
Margaret M. Gallaher, MD, Fern R. Hauck, MD, MS, Atlanta, Ga;
Miranda Yang-Oshida, RD, MPH, Mescalero, NM;
Mary K. Serdula, MD, MPH, Atlanta, Ga

Serum Lipid Concentrations in Subjects With Phenylketonuria and Their Families 1266
Terry J. DeClue, MD; Jim Davis, MD; Dawn M. Schocken, MPH;
Ruth Kangas, RD; Steve A. Benford, Tampa, Fla

Adolescent Pelvic Examination: An Effective Practical Approach 1269
Hyman C. Tolmas, MD, New Orleans, La

Acellular Pertussis Vaccines: Efficacy and Evaluation of Clinical Case Definitions 1285
William C. Blackwelder, PhD, Bethesda, Md; Jann Storsaeter, MD;
Patrick Olin, MD, PhD; Hans O. Hallander, MD, PhD, Stockholm, Sweden

Cardiopulmonary Exercise Testing in Children Following Surgery for Tetralogy of Fallot 1290
Teresa L. Tomassoni, PhD; Frank M. Galioto, Jr, MD, Washington, DC;
Paul Vaccaro, EdD, College Park, Md

Pediatric Germ Cell and Human Chorionic Gonadotropin–Producing Tumors: Clinical and Laboratory Features 1294
Anna T. Englund, MD; Mitchell E. Geffner, MD; Ronald A. Nagel, MD;
Barbara M. Lippe, MD; Glenn D. Braunstein, MD, Los Angeles, Calif

Direct Bilirubin Measurements in Jaundiced Term Newborns: A Reevaluation 1305
Thomas B. Newman MD, MPH, Sylvia Hope, PhD, San Francisco, Calif;
David K. Stevenson MD, Stanford, Calif

Continued on page 1219.

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Bone Mineral Content of Healthy, Full-term Neonates: Effect of Race, Gender, and Maternal Cigarette Smoking 1310
Pankaja S. Venkataraman, MBBS;
James C. Duke, PhD, Oklahoma City, Okla

Prevalence of Birth Defects Among Low-Birth-Weight Infants: A Population Study 1313
Fatima Mili, MD, MPH; Larry D. Edmonds, MSPH;
Muin J. Khoury, MD, PhD; Anne B. McClearn, Atlanta, Ga

Sudden Deaths and Apparent Life-Threatening Events in Hospitalized Neonates Presumed to Be Healthy 1319
David J. Burchfield, MD, Gainesville, Fla;
D. Jim Rawlings, MD, Jacksonville, Fla

EDUCATIONAL INTERVENTIONS

Comparison of a Computer Tutorial With Other Methods for Teaching Well-Newborn Care 1255
Larry W. Desch, MD; Maria T. Esquivel, MD;
Sharon K. Anderson, MA, Columbia, Mo

Current Trends in Pediatric Residency Training 1272
Carol Carraccio, MD, Alice Ackerman, MD, Baltimore, Md

SPORTS MEDICINE

Commotio Cordis: The Single, Most Common Cause of Traumatic Death in Youth Baseball 1279
Thomas J. Abrunzo, MD, Tampa, Fla

REVIEW

How Much of Neonatal Encephalopathy Is due to Birth Asphyxia? 1325
Karin B. Nelson, MD, Bethesda, Md; Alan Leviton, Boston, Mass

SPECIAL FEATURES

Radiological Case of the Month 1299
William G. Bennett, MD, Little Rock, Ark;
Beverly P. Wood, MD, Los Angeles, Calif

Picture of the Month 1301
Philip R. Cohen, MD, Adelaide A. Hebert, MD, Houston, Tex;
Murray Feingold, MD, Brighton, Mass;
Walter W. Tunnessen, Jr, MD, Philadelphia, Pa

CORRECTION

Intraosseous Infusion of Dobutamine and Isoproterenol 1312
John F. Bilello, MD, Washington, DC;
Kevin C. O'Hair, DVM, El Paso, Tex;
William C. Kirby, MD; John W. Moore, MD, Washington, DC

Evaluation of Intraosseous vs Intravenous Antibiotic Levels in a Porcine Model 1241
David G. Jaimovich, MD, Chicago, Ill; Ashir Kumar, MD, Lansing, Mich;
Steve Francom, PhD, Kalamazoo, Mich

REGULAR DEPARTMENTS

Instructions for Authors 1220

Classified Advertising 1334

Index to Advertisers 1214

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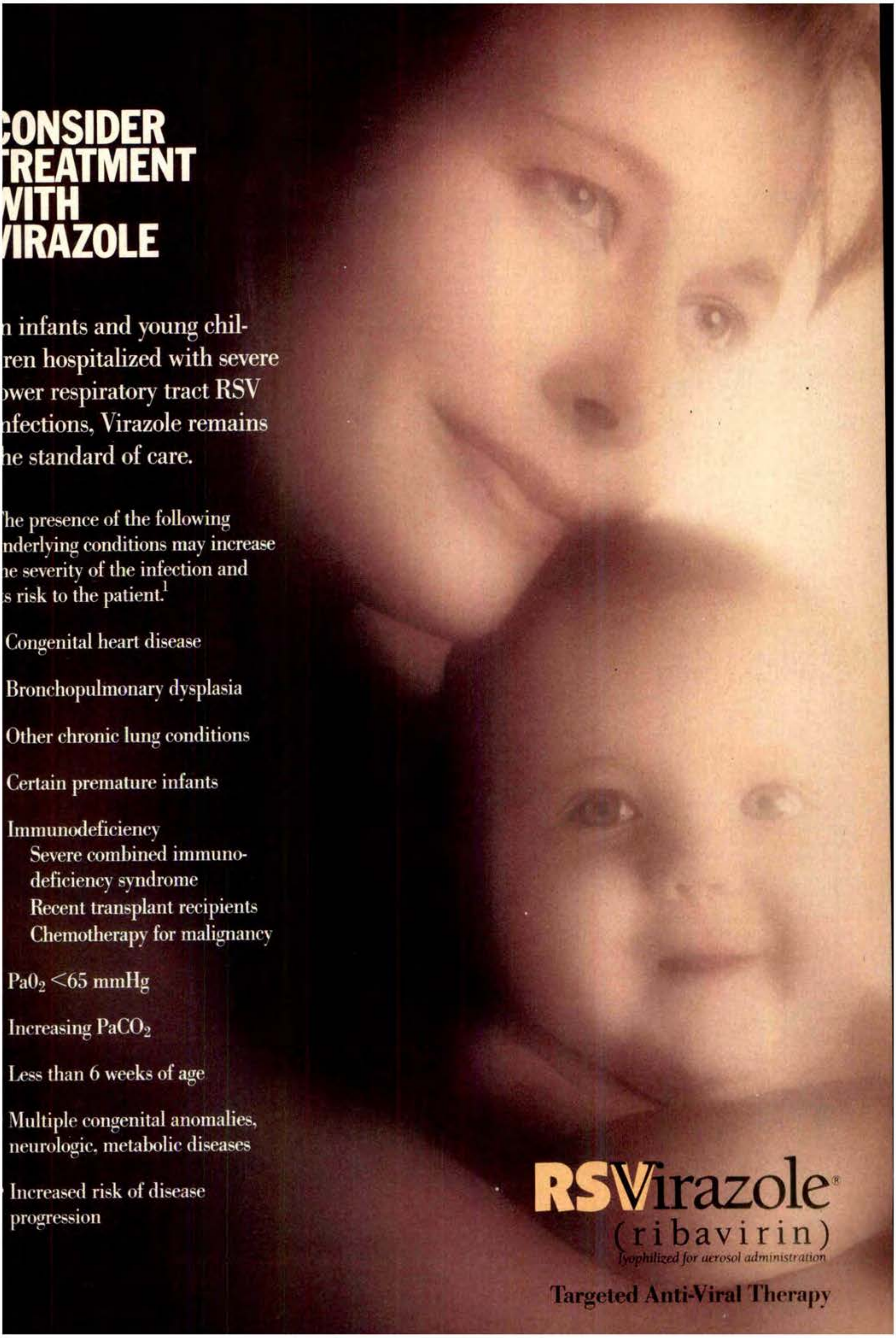

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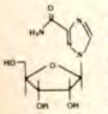

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CLINICAL PHARMACOLOGY:

Antiviral effects:

Ribavirin has antiviral inhibitory activity *in vitro* against respiratory syncytial virus,[1] influenza virus, and herpes simplex virus. Ribavirin is also active against respiratory syncytial virus (RSV) in experimentally infected cotton rats.[2]

In cell cultures, the inhibitory activity of ribavirin for RSV is selective. The mechanism of action is unknown. Reversal of the *in vitro* antiviral activity by guanosine or xanthosine suggests ribavirin may act as an analogue of these cellular metabolites.

Immunologic effects:

Neutralizing antibody responses to RSV were decreased in ribavirin treated compared to placebo treated infants.[3] The clinical significance of this observation is unknown. In rats, ribavirin resulted in lymphoid atrophy of thymus, spleen, and lymph nodes. Humoral immunity was reduced in guinea pigs and ferrets. Cellular immunity was also mildly depressed in animal studies.

Microbiology:

Several clinical isolates of RSV were evaluated for ribavirin susceptibility by plaque reduction in tissue culture. Plaques were reduced 85-98% by 16 μg/ml; however, plaque reduction varies with the test system. The clinical significance of these data is unknown.

Pharmacokinetics:

Assay for ribavirin in human materials is by a radioimmunoassay which detects ribavirin and at least one metabolite.

Ribavirin administered by aerosol is absorbed systemically. Four pediatric patients inhaling ribavirin aerosol administered by face mask for 2.5 hours each day for 3 days had plasma concentrations ranging from 0.44 to 1.55 μM, with a mean concentration of 0.76 μM. The plasma half-life was reported to be 9.5 hours. Three pediatric patients inhaling ribavirin aerosol administered by face mask or mist tent for 20 hours each day for 5 days had plasma concentrations ranging from 1.5 to 14.3 μM, with a mean concentration of 6.8 μM.

It is likely that the concentration of ribavirin in respiratory tract secretions is much higher than plasma concentrations in view of the route of administration.

The bioavailability of ribavirin aerosol is unknown and may depend on the mode of aerosol delivery. After aerosol treatment, peak plasma concentrations are less than the concentration that reduced RSV plaque formation in tissue culture by 85 to 98%. After aerosol treatment, respiratory tract secretions are likely to contain ribavirin in concentrations many fold higher than those required to reduce plaque formation. However, RSV is an intracellular virus and serum concentrations may better reflect intracellular concentrations in the respiratory tract than respiratory secretion concentrations.

In man, rats, and rhesus monkeys, accumulation of ribavirin and/or metabolites in the red blood cells has been noted, plateauing in red cells in man in about 4 days and gradually declining with an apparent half-life of 40 days. The extent of accumulation of ribavirin following inhalation therapy is not well defined.

INDICATIONS AND USAGE:

Ribavirin aerosol is indicated in the treatment of hospitalized infants and young children with severe lower respiratory tract infections due to respiratory syncytial virus (RSV). In two placebo-controlled trials in infants hospitalized with RSV lower respiratory tract infection, ribavirin aerosol treatment had a therapeutic effect, as judged by the reduction by treatment day 3 of severity of clinical manifestations of disease.[3,4] Virus titers in respiratory secretions were also significantly reduced with ribavirin in one of these studies.[4]

Only severe RSV lower respiratory tract infection is to be treated with ribavirin aerosol. The vast majority of infants and children with RSV infection have no lower respiratory tract disease or have disease that is mild, self-limited, and does not require hospitalization or antiviral treatment. Many children with mild lower respiratory tract involvement will require shorter hospitalization than would be required for a full course of ribavirin aerosol (3 to 7 days) and should not be treated with the drug. Thus the decision to treat with ribavirin aerosol should be based on the severity of the RSV infection.

The presence of an underlying condition such as prematurity or cardiopulmonary disease may increase the severity of the infection and its risk to the patient. High risk infants and young children with these underlying conditions may benefit from ribavirin treatment, although efficacy has been evaluated in only a small number of such patients.

Ribavirin aerosol treatment must be accompanied by and does not replace standard supportive respiratory and fluid management for infants and children with severe respiratory tract infection.

Diagnosis:

RSV infection should be documented by a rapid diagnostic method such as demonstration of viral antigen in respiratory tract secretions by immunofluorescence[3,4] or ELISA[5] before or during the first 24 hours of treatment. Ribavirin aerosol is indicated only for lower respiratory tract infection due to RSV. Treatment may be initiated while awaiting rapid diagnostic test results. However, treatment should not be continued without documentation of RSV infection.

CONTRAINDICATIONS:

Ribavirin is contraindicated in women or girls who are or may become pregnant during exposure to the drug. Ribavirin may cause fetal harm and respiratory syncytial virus infection is self-limited in this population. Ribavirin is not completely cleared from human blood even four weeks after administration. Although there are no pertinent human data, ribavirin has been found to be teratogenic and/or embryolethal in nearly all species in which it has been tested. Teratogenicity was evident after a single oral dose of 2.5 mg/kg in the hamster and after daily oral doses of 10 mg/kg in the rat. Malformations of skull, palate, eye, jaw, skeleton, and gastrointestinal tract were noted in animal studies. Survival of fetuses and offspring was reduced. The drug causes embryolethality in the rabbit at daily oral dose levels as low as 1 mg/kg.

WARNINGS:

Ribavirin administered by aerosol produced cardiac lesions in mice and rats after 30 and 36 mg/kg, respectively, for 4 weeks, and after oral administration in monkeys at 120 and rats at 154 to 200 mg/kg for 1 to 6 months. Ribavirin aerosol administered to developing ferrets at 60 mg/kg for 10 or 30 days resulted in inflammatory and possible emphysematous changes in the lungs. Proliferative changes were seen at 131 mg/kg for 30 days. The significance of these findings to human administration is unknown.

Ribavirin lyophilized in 6 gram vials is intended for use as an aerosol only.

PRECAUTIONS:

General:

Patients with lower respiratory tract infection due to respiratory syncytial virus require optimum monitoring and attention to respiratory and fluid status.

Drug Interactions:

Interactions of ribavirin with other drugs such as digoxin, bronchodilators, other antiviral agents, antibiotics, or antimetabolites has not been evaluated. Interference by ribavirin with laboratory tests has not been evaluated.

Carcinogenesis, mutagenesis, impairment of fertility:

Ribavirin induces cell transformation in an *in vitro* mammalian system (Balb/C3T3 cell line). However, *in vivo* carcinogenicity studies are incomplete. Results thus far, though inconclusive, suggest that chronic feeding of ribavirin to rats at dose levels in the range of 16-60 mg/kg body weight can induce benign mammary, pancreatic, pituitary and adrenal tumors.

Ribavirin is mutagenic to mammalian (L5178Y) cells in culture. Results of microbial mutagenicity assays and a dominant lethal assay (mouse) were negative.

Ribavirin causes testicular lesions (tubular atrophy) in adult rats at oral dose levels as low as 16 mg/kg/day (lower doses not tested), but fertility of ribavirin-treated animals (male or female) has not been adequately investigated.

Pregnancy:

Teratogenic Effects: Pregnancy Category X. See "Contraindications" section.

Nursing Mothers: Use of ribavirin aerosol in nursing mothers is not indicated because RSV infection is self-limited in this population. Ribavirin is toxic to lactating animals and their offspring. It is not known whether the drug is excreted in human milk.

ADVERSE REACTIONS:

Approximately 200 patients have been treated with ribavirin aerosol in controlled or uncontrolled clinical studies.

Pulmonary function significantly deteriorated during ribavirin aerosol treatment in six of six adults with chronic obstructive lung disease and in four of six asthmatic adults. Dyspnea and chest soreness were also reported in the latter group. Minor abnormalities in pulmonary function were also seen in healthy adult volunteers.

Several serious adverse events occurred in severely ill infants with life-threatening underlying diseases, many of whom required assisted ventilation. The role of ribavirin aerosol in these events is indeterminate. The following events were associated with ribavirin use:

Pulmonary: Worsening of respiratory status, bacterial pneumonia, pneumothorax, apnea, and ventilator dependence.

Cardiovascular: Cardiac arrest, hypotension, and digitalis toxicity.

There were 7 deaths during or shortly after treatment with ribavirin aerosol. No death was attributed to ribavirin aerosol by the investigators.

Some subjects requiring assisted ventilation have experienced serious difficulties, which may jeopardize adequate ventilation and gas exchange. Precipitation of drug within the ventilatory apparatus, including the endotracheal tube, has resulted in increased positive end expiratory pressure and increased positive inspiratory pressure. Accumulation of fluid in tubing ("rain out") has also been noted.

Although anemia has not been reported with use of the aerosol, it occurs frequently with oral and intravenous ribavirin, and most infants treated with the aerosol have not been evaluated 1 to 2 weeks post-treatment when anemia is likely to occur. Reticulocytosis has been reported with aerosol use.

Rash and conjunctivitis have been associated with the use of ribavirin aerosol.

Overdosage:

No overdosage with ribavirin by aerosol administration has been reported in the human. The LD_{50} in mice is 2 gm orally. Hypoactivity and gastrointestinal symptoms occurred. In man, ribavirin is sequestered in red blood cells for weeks after dosing.

DOSAGE AND ADMINISTRATION:

Before use, read thoroughly the Viratek Small Particle Aerosol Generator (SPAG) Model SPAG-2 Operator's Manual for small particle aerosol generator operating instructions.

Treatment was effective when instituted within the first 3 days of respiratory syncytial virus lower respiratory tract infection.[3] Treatment early in the course of severe lower respiratory tract infection may be necessary to achieve efficacy.

Treatment is carried out for 12-18 hours per day for at least 3 and no more than 7 days, and is part of a total treatment program. The aerosol is delivered to an infant oxygen hood from the SPAG-2 aerosol generator. Administration by face mask or oxygen tent may be necessary if a hood cannot be employed (see SPAG-2 manual). However, the volume of distribution and condensation area are larger in a tent and efficacy of this method of administering the drug has been evaluated in only a small number of patients. Ribavirin aerosol is not to be administered with any other aerosol generating device or together with other aerosolized medications. Ribavirin aerosol should not be used for patients requiring simultaneous assisted ventilation (see Boxed Warnings).

Virazole is supplied as 6 grams of lyophilized drug per 100 ml vial for aerosol administration only. By sterile technique, solubilize drug with sterile USP water for injection or inhalation in the 100 ml vial. Transfer to the clean, sterilized 500 ml widemouth Erlenmeyer flask (SPAG-2 Reservoir) and further dilute to a final volume of 300 ml with sterile USP water for injection or inhalation. The final concentration should be 20 mg/ml. **Important:** This water should not have had any antimicrobial agent or other substance added. The solution should be inspected visually for particulate matter and discoloration prior to administration. Solutions that have been placed in the SPAG-2 unit should be discarded at least every 24 hours and when the liquid level is low before adding newly reconstituted solution.

Using the recommended drug concentration of 20 mg/ml ribavirin as the starting solution in the drug reservoir of the SPAG unit, the average aerosol concentration for a 12 hour period would be 190 micrograms/liter (0.19 mg/l) of air.

HOW SUPPLIED:

Virazole® (ribavirin) Aerosol is supplied in 100 ml glass vials with 6 grams of sterile, lyophilized drug which is to be reconstituted with 300 ml sterile water for injection or sterile water for inhalation (no preservatives added) and administered only by a small particle aerosol generator (SPAG-2). Vials containing the lyophilized drug powder should be stored in a dry place at 15-25°C (59-78°F). Reconstituted solutions may be stored, under sterile conditions, at room temperature (20-30°C, 68-86°F) for 24 hours. Solutions which have been placed in the SPAG-2 unit should be discarded at least every 24 hours.

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ADVERTISING REFERENCES:

1. Adapted from "Policy statement. Ribavirin therapy of respiratory syncytial virus." American Academy of Pediatrics Committee on Infectious Diseases. 1986-87.

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ICN Pharmaceuticals, Inc.
ICN Plaza
3300 Hyland Avenue
Costa Mesa, CA 92626
Telephone: (714) 545-0100

Call for Abstracts

The American Pediatric Society and The Society for Pediatric Research announce that the abstract deadline for the 1992 Annual Meeting (May 4-7, 1992, Convention Center, Baltimore, Md) has been set as *January 3, 1992*. For further information, contact the APA Headquarters, 6728 Old McLean Village Dr, McLean, VA 22101 ([703]556-9222; FAX [703]556-8729), or the APS/SPR Association . . . . ([708]427-0205; FAX [708] 427-1305).

Sudden Cardiac Death

Sir.—The otherwise excellent review of sudden cardiac death in young athletes by McCaffrey and colleagues[1] is marred by misstatement of the inheritance of the long QT syndromes. The Jervell and Lange-Nielson syndrome[2] is autosomal recessive and accompanied by congenital deafness. The Romano-Ward syndrome[3,4] has an autosomal dominant inheritance and is accompanied by normal hearing. Many family studies have confirmed these patterns of inheritance.[5]

William Pearl, MD
William Beaumont Army
Medical Center
Division of Pediatric Cardiology
Box 70614
El Paso, TX 79920

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Staphylococcus aureus in Impetigo

Sir.—Demidovich et al[1] recently published the results of a study comparing penicillin, erythromycin, and cephalexin therapies for impetigo. This study has to be praised, since a lot of confusion still exists with regard to childhood impetigo. Two of their conclusions were that *Staphylococcus aureus* was the most common cause of impetigo in children in their population and that penicillin is an inadequate treatment for this infection.

Sixteen months earlier, I and a coauthor published our results of a study comparing amoxicillin with augmentin for the treatment of nonbullous impetigo.[2] In our population in southern Israel, *S aureus* was isolated from 100% of the patients, while additional streptococci were isolated from 29%. All 51 isolates of *S aureus* were resistant to penicillin; treatment failure was observed in five (20%) of 25 patients who received amoxicillin compared with none of those who received augmentin. Our conclusions, as follows, were similar to those expressed by Demidovich et al. "We conclude that in areas where *Staphylococcus aureus* is usually penicillin resistant, the empiric therapy of impetigo should include a drug that is active against both staphylococci and streptococci."[2]

It is surprising that our article, published in the same journal, was not cited in the report by Demidovich et al. Such a citation from a different geographical region could strengthen their conclusions.

Ron Dagan, MD
Pediatric Infectious
Disease Unit
Soroka University
Medical Center
PO Box 151
Beer-Sheva, Israel

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In Reply.—I am sorry that we missed the report by Dagan and Bar-David. It was published a few months before our study was submitted for publication, so we did not find it in our review. We did cite two other recent studies from the southeastern and southwestern United States that showed, along with our study, that penicillin-resistant *Staphylococcus aureus* is emerging as the major pathogen implicated as the cause of impetigo in diverse areas of the United States. The report by Dagan and Bar-David, along with an extensive review of the cause of impetigo from numerous other reports summarized by Esterly et al[1] in a more recent issue of *AJDC*, confirms that this is a worldwide phenomenon. From these observations, it may be concluded that penicillin is no longer adequate for primary treatment of impetigo in most areas of the world.

James W. Bass, MD
Department of Pediatrics
Tripler Army Medical Center
Honolulu, HI 96859-5000

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Treatment Withdrawal in Neonates

Sir.—The recent article by Young and Stevenson[1] describes the Stanford "individualized prognostic strategy" approach to aggressive support in the neonatal intensive care unit as the exception to the American norm. If this statement is indeed valid, it is a sad reflection on neonatal intensive care in the United States. The authors ask why there is such difficulty in stopping aggressive therapy, and suggest fear of litigation as a likely cause. Although such decision making is in an area of uncertainty, this should not prevent a decision from being reached. Physicians in training, particularly in acute care areas, must be taught that good clinical decisions cannot always be made with certainty. Clinical judgments are made in the best interest of the patient without any guarantee of certainty. The physician's responsibility must be to inform the family of the risks and benefits of treatment and to help formulate a plan to treat or to withdraw. If we continue to erode this responsibility or confuse it with medical paternalism, then we will become a profession of technicians rather than caring physicians. It is taking the easy way out to make a nondecision to treat every baby aggressively until multiple system failure develops on the respirator. As Campbell[2] has stated, ". . . taking these decisions are supreme tests of medical leadership." The acceptance of such decisions depends on mutual trusting that the doctors and the parents are putting the infant's interests above their own. If that trust does not exist within the neonatal intensive care unit, then the best interests of the infants will not be served. Surely "individualized prognostic strategy" simply means treating each patient and family with the care and dignity that they deserve and involves the practice of "close-up" ethics vs "distant" ethics as described by Duff.[3]

PAUL BYRNE, MB, CHB, FRCPC
R. WELCH, MB, CHB, MRCP
University of Alberta Hospitals
2C300 Walter V. Mackenzie Health Sciences Center
Edmonton, Alberta,
Canada T6G 2R7

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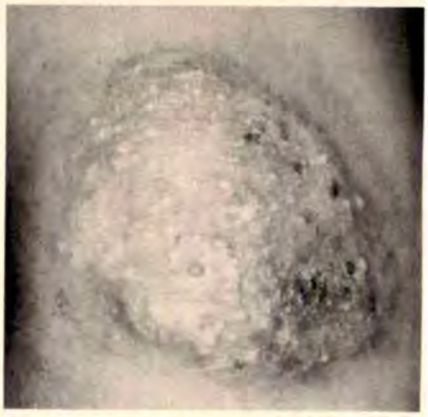
Exacerbation of Tinea Corporis During Treatment With 1% Clotrimazole/0.05% Betamethasone Dipproprionate (Lotrisone)

Sir.—An 8-year-old girl with tinea corporis of the knee was treated with a combination product of 1% clotrimazole and 0.05% betamethasone dipproprionate cream (Lotrisone). She had a prolonged course, with persistent pustules and inflammation that permanently scarred her knee. The histologic appearance was that of a Majocchi's granuloma, a fungal dermal abscess similar to a kerion. We postulate that the cause was local immunosuppression by the fluorinated steroid in this cream.

Patient Report.—Eleven weeks before presentation, an 8-year-old girl had played in a barn in which many cats made their home. Nine weeks before presentation, she developed an erythematous, ring-shaped, scaly lesion on her right knee, diagnosed by her family physician as "ringworm." A combination cream containing 1% clotrimazole and 0.05% betamethasone dipproprionate was prescribed to be applied twice daily until the lesion resolved.

The cream was faithfully applied without occlusion for 9 weeks, but instead of resolving, the plaque enlarged, became bright red, boggy, pustular, tender, and covered with a serous exudate (Figure). The patient developed knee pain and had difficulty walking. She was brought to one of us (R.D.R.), and cellulitis was considered. The Lotrisone treatment was discontinued. A short course of oral cefadroxil monohydrate failed to heal the lesion.

The patient was seen in the Pediatric Dermatology Clinic at the Childrens Hospital Medical Center, Cincinnati, Ohio. Physical examination revealed a 10-cm tender, boggy, erythematous, pustular, exophytic plaque on the right knee. A diagnosis of tinea corporis with Majocchi's granuloma formation was made. A potassium hydroxide (KOH) preparation showed long branching septate hyphae and spores, and a culture of tissue obtained at skin biopsy yielded *Trichophyton mentagrophytes.* Histologic examination confirmed the presence of a dermal abscess with occasional yeast forms identified in the base of hair follicles.



Majocchi's granuloma (fungal dermal abcess) on the right knee of an 8-year-old girl. The lesion developed during a 9-week treatment of tinea corporis with a combination product of 1% clotrimazole and 0.05% betamethasone dipproprionate cream (Lotrisone).

The patient was treated with a course of oral microsize griseofulvin (15 mg/kg per day). Six weeks later, she walked without a limp but a culture was still positive for *T mentagrophytes.* At 8 weeks, the lesion had become flat, nearly flesh colored, and studded with 1- to 3-mm depressed scars at the sites of previous pustules. Fungal culture of the surface was sterile. Two and a half years later, the child has a permanently scarred knee.

Comment.—It is well documented that potent topical steroids applied alone may enhance fungal growth on the skin.[1,2] In one case report of an adverse effect of 1% clotrimazole/0.05% betamethasone dipproprionate cream, an adult patient was not only unable to resolve a tinea corporis, but also developed significant striae from the combination's potent steroid. Simply switching to 1% clotrimazole cream (Lotrimin) afforded her brisk resolution of the tinea.[3] We describe this patient to alert physicians that combination creams containing both an antifungal and a potent fluorinated corticosteroid may enhance fungal growth to the point of Majocchi's granuloma formation.

The clinical and histologic appearance of our patient's knee lesion, ie, follicular pustules with intradermal abscess formation, was that of a Majocchi's granuloma. It is quite similar to a kerion, which is usually seen only on the scalp. We postulate that the potent anti-inflammatory action of the 0.05% betamethasone dipproprionate in Lotrisone caused local immunosuppression such that both the antifungal activity of clotrimazole and local cell-mediated immunity were overwhelmed.

The steroid in Lotrisone is a class III fluorinated compound, betamethasone diproprionate (Diprosone).[4] Food and Drug Administration labeling for Lotrisone warns against its use for more than 2 weeks to treat tinea corporis and against use under occlusion. It is not approved for use in children under age 12 years. We suspect that few physicians and pharmacists are aware of, or inform patients of, these caveats.

Application of such a potent topical steroid to areas such as the perineum, especially with occlusion (eg, treating monilial diaper dermatitis) could potentially lead to cutaneous atrophy and stria formation. Systemic absorption of steroids from the perineum can be very high, leading to the possibility of adrenal suppression.[5]

Fluorinated topical steroid/antifungal combinations should not be used for conditions in which a simple topical antifungal, with or without the concomitant short-term use of a mild nonfluorinated topical steroid, would suffice.

Reprint requests to New Richmond Family Practice, 1050 Old US 52, New Richmond, OH 45157 (Dr Reynolds).

RONALD D. REYNOLDS, MD
New Richmond Family
Practice
1050 Old US 52
New Richmond, OH 45157
SUSAN BOIKO, MD
Department of Dermatology
University of Cincinnati
College of Medicine
Cincinnati, OH 45267
ANNE W. LUCKY, MD
Dermatology Clinic
Childrens Hospital
Medical Center
Cincinnati, OH 45267

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Mediterranean Visceral Leishmaniasis: A Frequently Unrecognized Imported Disease

Sir.—Visceral leishmaniasis is endemic in countries surrounding the Mediterranean Sea. With mass tourism, nonresidents returning from this area are now also increasingly affected.[1,2] However, it appears from the literature that this diagnosis is often not considered in these patients, that numerous unnecessary investigations are performed, and that appropriate treatment of this potentially fatal infection is delayed or withheld.[3] This is clearly illustrated by the following report.

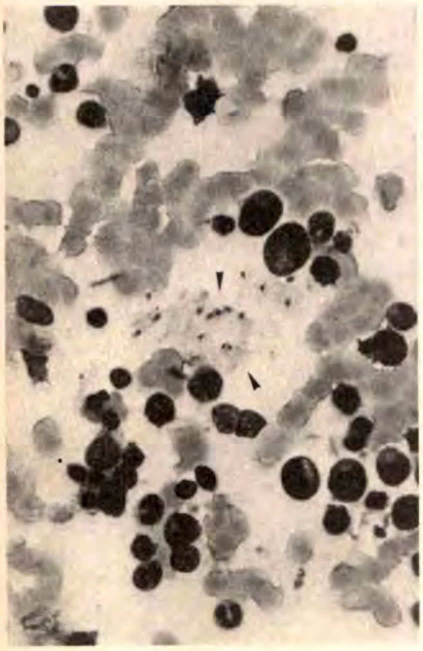
Patient Report.—A 10-month-old boy was referred to our department because of a persistent spiking fever of 3 weeks' duration that had not responded to oral treatment with amoxicillin and cefadroxil. Clinical investigation on admission revealed a fever of 40°C, marked hepatosplenomegaly, paleness, and slightly enlarged inguinal lymph nodes. Abnormal results of laboratory investigation were severe hypochromic anemia, leukopenia with neutropenia, thrombocytopenia, increased C-reactive protein levels, and positive results of a direct Coombs' test (Table). Roentgenograms of the chest and results of a tuberculin skin test as well as several blood and urine cultures, remained negative. Results of bone marrow aspiration showed generalized hypercellularity, normal megakaryocytes, a normal leukocyte series, and hypochromic erythroid hyperplasia. A computed tomographic scan showed bilateral accumulation of fluid in the middle ear and mastoid cavity. The diagnosis of mastoiditis was made, and intravenous treatment with sodium cefotaxime and amikacin sulfate was started. A blood transfusion was also performed.

During the following weeks, the clinical symptoms persisted, and the patient's general condition deteriorated. Laboratory investigation confirmed pancytopenia, a low serum albumin value, hypergammaglobulinemia, and increased C-reactive protein values, but now also revealed oligoclonal gammopathy, antinuclear antibodies, and increased circulating IgG immune complexes. Serum C3

Laboratory Values Associated With Leishmaniasis*

Sample Components	Week 1	Component Values During Antimony Treatment at Week 3	5	7	Week 11	Normal Values
Erythrocytes, x10¹²/L	2.67	2.50	3.22	3.40	3.84	3.7-5.3
Hemoglobin, g/L	55	56	85	97	103	90-140
Leukocytes, x10⁹/L	3.5	2.3	8.5	6.9	8.5	6.0-17.5
Neutrophils, x10⁹/L	0.66	0.16	1.14	1.33	1.98	1.5-3.0
Platelets, x10⁹/L	93	50	361	292	242	150-400
Albumin, g/L	40	27	38	42	47	40-50
Total protein, g/L	68	64	88	82	82	50-70
IgG, g/L	14.39	18.26	33.79	27.70	21.27	2.79-15.33
IgM, g/L	1.31	1.01	6.97	3.26	1.29	.22-1.47
CRP, g/L	.068	.1202	.0063	.0028	.0028	.0028
ANA	1/80	1/320	1/320	1/640	1/80	Negative

*CPR indicates C-reactive protein, and ANA, antinuclear antibodies. Albumin, total protein, IgG, IgM, CRP, and ANA values are from serum samples. ANA values are given as liters.



Photomicrograph of bone marrow aspirate showing amastigote forms of leishmania and disrupted macrophage (arrows) (May-Giemsa-Grünwald, original magnification × 1000).

and C4 and total hemolytic complement values were within normal limits, and results of extractable nuclear antigen, rheumatoid factor, and Rose-Waaler tests were negative. Still's disease was tentatively diagnosed, and treatment with oral aspirin (100 mg/kg of body weight per day) was started. This treatment lowered the patient's temperature and decreased the frequency of temperature spikes, but his general condition did not improve, and hepatosplenomegaly and pancytopenia persisted. Finally, attention was drawn to the fact that the family had spent 3 weeks in Barcelona, Spain, 8 months before the patient's admission to our facility and had regularly visited the beach. The previously performed bone marrow aspirate was carefully reinvestigated using a higher magnification (original magnification ×1200). Amastigote forms of *Leishmania* were seen extracellularly and within some macrophages (Figure). Intravenous sodium stibogluconate (Pentostam) was administered at a dose of 20 mg/kg of body weight per day for 30 days. Hepatosplenomegaly slowly regressed, but a residual splenomegaly of 5 cm persisted at the end of treatment. The patient's general condition markedly improved. C-reactive protein and peripheral blood cell values gradually normalized, but levels of antinuclear antibodies and serum IgG and IgM increased during treatment. Except for some flattening of T waves on electrocardiogram, no adverse reactions of therapy were seen.

Comment.—Mediterranean visceral leishmaniasis is caused by the protozoan *Leishmania donovani infantum* and is transmitted from animals, especially dogs, by the sand fly (*Phlebotomus* species). The disease affects mainly children; 80% of those affected are younger than age 5 years. The typical clinical presentation consists of persistent irregular fever, hepatosplenomegaly, hemolytic anemia (which is often severe), neutropenia, agranulocytosis with relative monocytosis, and thrombocytopenia that seldom causes a tendency to bleed[4] (pseudoleukemic pattern). Immunologic abnormalities such as positive results of direct Coombs' and Rose-Waaler tests and of tests to detect rheumatoid factor and antinuclear antibodies, increased levels of circulating immune complexes, and hypergammaglobulinemia have been observed.[5,6] The pathogenesis of these abnormalities has now been elucidated.[7,8]

Mediterranean visceral leishmaniasis has often been confused with other diseases with more or less similar clinical presentations, mainly, chronic bacterial or viral infections[9] and autoimmune diseases.[10] In many cases, malignant neoplasms were initially suspected. In others, pancytopenia was ascribed to the previous use of medications such as chloramphenicol.[11] Some patients underwent splenectomy for presumed idiopathic hypersplenism.[12,13] Leishmaniasis should be suspected in patients, mainly children, who visited Mediterranean countries and who present with one or more of the forementioned clinical symptoms, especially the pseudoleukemic pattern of hepatosplenomegaly and pancytopenia. It is important to note that incubation may vary from 3 months to more than 2 years, an aspect that was not considered in our patient. The diagnosis is based on the investigation of a bone marrow aspirate with the usual May-Giemsa-Grünwald or Giemsa stains using a magnification of at least ×1000. The ovoid protozoa appear in the cytoplasm of macrophages or extracellularly as clusters of 2- to 3-μm particles with large, eccentric, reddish nuclei, small kinetoplasts, and bluish cytoplasms. When a lower magnification is used, as in this case, or when experience with laboratory diagnosis of tropical conditions is lacking,[14] the protozoa may easily be mistaken for dust or inclusion bodies in the macrophages. The diagnosis can be confirmed with an indirect hemagglutination test, a complement fixation test, a highly sensitive indirect immunofluorescence antibody test, and highly specific immunoelectrophoretic techniques.[15]

The treatment of choice of Mediterranean visceral leishmaniasis is intramuscular or intravenous administration of pentavalent antimony compounds (either sodium stibogluconate [Pentostam] or meglumine antimoniate [Glucantine]) at a dose of 20 mg/kg of body weight per day for at least 14 days after negative results of bone marrow aspiration are obtained. Pentamidine, amphotericin B, and allopurinol may be used when antimony therapy is unsuccessful or contraindicated.[16] Treatment, such as blood transfusions and administration of antipyretic agents, should be given to alleviate symptoms. Splenectomy has been performed in drug-resistant cases.[17] In most instances, treatment with antimony results in resolution of fever, pancytopenia, and hepatosplenomegaly in that order. The latter, however, may persist for months. The immunologic abnormalities also disappear progressively, but hypergammaglobulinemia and autoimmune antibodies may persist for months. Postinfectious immunity is the rule, but relapses occur, mostly within 2 years.

Ludo M. Mahieu, MD
Karel J. Van Acker, MD, PhD
Department of Pediatrics
University Hospital of Antwerp
Wilrijkstraat 10
B-2650 Antwerpen, Belgium

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Send Linus to Me

Sir.—I read about Friman's[1] research in the *Toronto Daily Star* and would like to explain how I get thumb-sucking children to stop. I teach parenting in a Toronto high school and direct a small on-site nursery laboratory center for 3-year-old children.

Thumb-sucking is discussed as something one does at home, in one's bed, usually when sleepy. I explain that since we have no bed at school, I will arrange a little corner as a bed, and if I see children sucking their thumbs, I let them rest there.

I ask the child, "Are you still sleepy, do you need to rest some more?" The response is usually "no," and the thumb comes out. The second time this happens I say, "I see you are still tired," and I lead the child to the "little bed" and say "When you are finished sucking your thumb, come back and join us." Thumb-sucking usually stops in 1 day. I do this in January, after the children have been in school 4 months.

I explain beforehand to the parents what I will do and try this method only with their consent. Parents are thrilled with this method because they usually have found the child unresponsive during thumb-sucking and are happy to have a real person around instead of a "zombie" kid.

I have been teaching this type of class for 16 years. During this time I have also led parent study groups using *Children: The Challenge,* by Dreikurs.[2]

I have confidence in this method and encourage physicians and parents to try it.

HARRIET SZONYI
336 St Clair Ave E
Toronto, Ontario,
Canada M4T 1P4

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In Reply.—I appreciate Szonyi's comments on her method of treating thumb-sucking, which certainly seems successful. Missing, of course, are supportive data, but she is not offering her comments as a scientific report. Should she need empirically derived support for her method, she need go no further than the nearest behavioral journal focused on analysis, modification, or therapy. Her method sounds similar to "time-out," a procedure involving contingent removal from reinforcing conditions. Time-out has been used effectively for a variety of child behavior problems and its use is often discussed in behavioral journals.

The primary advantage of the method I described is its privacy. Use of Szonyi's method makes a child's thumb-sucking and its treatment public. Given the potential risk that chronic thumb-sucking poses to self-esteem, a health care provider should weigh carefully the potential costs and benefits of such public intervention.

Finally, Szonyi's letter is something of a non sequitur because it addresses an issue that was not primary in my article, ie, treatment for thumb-sucking. The primary issue in my article was covariation between thumb-sucking and attachment to objects. The central question was what happens to attachment when thumb-sucking is treated? Still, I am interested in Szonyi's method. I would be even more interested in knowing what effect her treatment for thumb-sucking has on concurrent attachment in children who exhibit both behaviors.

PATRICK C. FRIMAN, PHD
Children's Hospital of
Philadelphia
Children's Seashore House
34th St & Civic Center Blvd
Philadelphia, PA 19104

A Markedly Immature Lecithin-Sphingomyelin Ratio at Term and Congenital Hypothyroidism

Sir.—A delay in pulmonary maturity and immature fetal lung profiles in infants born at term have been described in diabetic pregnancies.[1] This case report and review of neonatal screening results show that a markedly immature lecithin-sphingomyelin (L-S) ratio at term may be a prenatal marker for congenital hypothyroidism.

Patient Reports.—PATIENT 1.—A 25-

year-old gravida 2 woman with normal glucose screen results was admitted at 32 weeks' gestation with a diagnosis of a bleeding placenta previa. The bleeding resolved, and beginning at 35 weeks, weekly amniocentesis was performed for fetal lung profiles to ascertain pulmonary maturity as outlined by Kulovich et al.[2] The amniotic fluid L-S ratio never exceeded one and phosphatidyl glycerol was never detected. In spite of this the infant was electively delivered at 40.5 weeks. The infant developed respiratory distress syndrome (RDS), which required intubation and mild ventilatory support. The thyrotropin level was 718 mU/L and the thyroxine (T_4) level was 15.2 nmol/L. The infant was diagnosed as having congenital hypothyroidism.

PATIENT 2.—A 25-year-old gravida 4 woman with normal prenatal glucose screen results underwent an amniocentesis for a fetal lung profile at 37 weeks' gestation because of a history of classic cesarean sections. The L-S ratio was markedly immature and measured on a weekly basis until 41 weeks. The ratio never exceeded 1.3, and phosphatidyl glycerol was not detected. The infant was delivered at 41.5 weeks and did not show any signs of respiratory distress. The thyrotropin level was 496 mU/L and the T_4 level was 60.5 nmol/L. The infant was diagnosed as having agenesis of the thyroid.

Comment.—There were 9188 live births at our institution between January 1, 1987, and December 1, 1989. Of those births, 7258 occurred after 37 weeks' gestation as defined by American College of Obstetricians and Gynecologists criteria.[3] Amniocentesis was performed on 204 of the 7258 term patients for assorted indications. Two of the 204 patients had markedly immature L-S ratios at term. The predictive value of the fetal lung profile for RDS at our institution was similar to that described by Kulovich et al.[1,2] Analysis of the neonatal blood screening performed by the Metabolic Unit of the Missouri Department of Health revealed two cases of abnormal T_4 and thyrotropin levels. Both of these patients were the infants with markedly immature fetal lung profiles. This suggests a correlation between a markedly low L-S ratio at term and congenital hypothyroidism.

Delayed fetal lung maturity has been well described in diabetic pregnancies. This delay can manifest itself as either a delay in the phospholipid maturity indexes or the development of RDS in the presence of a mature L-S ratio. Neonatal respiratory distress has also been described in an infant with a mature L-S ratio and present phosphatidyl glycerol.[4] This infant ultimately proved to have congenital hypothyroidism. Our data show that congenital hypothyroidism may also be associated with immature fetal lung maturation indexes at term. The role of thyroxine in the development of surfactant has been shown in a number of animal models.[5,6] This mechanism has been used to implement the acceleration of maturation of the fetal lung in utero. Intra-amniotic thyroxine and maternally administered protirelin (thyrotropin-releasing hormone) have been shown to accelerate the maturation of the fetal lung profile.[7,8]

Congenital hypothyroidism can have a devastating effect on the neurologic development of the fetus and neonate. Unfortunately, few infants affected with congenital hypothyroidism show overt signs at birth.[9] Newborn screening can take weeks between the initial testing and confirmation. This delay in diagnosis and treatment can significantly alter the potential intellectual development of the infant. Amniocentesis or percutaneous umbilical blood sampling as screening methods are not justified on the basis of their cost and risk for a disorder, with an incidence of one in 5000 births.

In summary, an immature L-S ratio accompanied by absent phosphatidyl glycerol can be indicative of potential congenital hypothyroidism. We do not recommend performing amniocentesis as a primary screening method in a low-risk patient. According to our data, if a markedly immature fetal lung profile is present at term, further workup is necessary to rule out congenital hypothyroidism.

GARY R. COHEN, MD
JAMES THORP, MD
JOHN D. YEAST, MD
BRUCE A. MEYER, MD
St Luke's Perinatal Center
University of Missouri—
Kansas City
RICHARD O'KELL, MD
CANDACE MACY
Department of Laboratory
Medicine
St Luke's Hospital
St Luke's Perinatal
Center, OPC-2
44th and Wornall Rd
Kansas City, MO 64111

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Is Prophylaxis of Neonates With Intravenous Immunoglobulin Beneficial?

See also p 1233.

The human neonate, and especially the premature neonate, is uniquely susceptible to overwhelming bacterial infection. There are a variety of host defense abnormalities in neonates that aid in explaining this phenomenon, including deficiencies in specific antibodies, decreased levels of complement components, abnormalities in the function and number of neutrophils, and deficient T lymphocyte activity.[1] Until very recently, the only "gun" in the immunologist's or neonatologist's armamentarium for correcting these host defense abnormalities was immunoglobulin. This, coupled with the rather striking hypogammaglobulinemia observed in premature infants, led many investigators to examine the prophylactic role of immunoglobulin administration in preventing infections in neonates. Early anecdotal information or reports from small, uncontrolled trials suggested that the administration of intravenous immunoglobulin could prevent infection in premature infants weighing less than 1500 g.[1]

These early trials, which were conducted outside the United States, consisted of small numbers of patients (78 to 150), were not blinded or placebo-controlled, and often examined infections due to bacteria that are uncommon in US neonatal intensive care units. Thus, the results could not be extrapolated to use in this country. This prompted several large, controlled trials of the prophylactic use of intravenous immunoglobulin in neonates in the United States. To date, the preliminary reports of the results of these trials do not convincingly answer the question of the efficacy of intravenous immunoglobulin in the prophylaxis of bacterial infection. For instance, an initial report by Bussel and coworkers[2] of a double-blind, placebo-controlled trial of intravenous immunoglobulin in infants weighing less than 1300 g, as well as a verbal follow-up report at a recent National Institutes of Health Consensus Conference on intravenous immunoglobulin, failed to show a significant prophylactic effect against infection.

In contrast, Baker and associates,[3] in a large, multicenter, controlled trial (577 assessable patients), reported that the prophylactic administration of intravenous immunoglobulin to infants weighing 1500 g or less (500 mg/kg of body weight administered 3 to 7 days after birth, 1 week later, and then every 14 days) resulted in an overall reduction in infections of approximately 30%. Mortality was not significantly reduced in those given the immunoglobulin (3.5%) compared with those given the placebo (4.4%). There was, however, a reduction in hospital stay of 7 days (69 days in the group that received immunoglobulin vs 76 days in the group that received the placebo) and a significant reduction in severe necrotizing enterocolitis in immunoglobulin recipients. The most common microbial isolate in this study was *Staphylococcus epidermidis* (37%), followed by *Staphylococcus aureus* (20%). *Klebsiella* (14%) was the third most frequent isolate, while enterococci were fourth (11%).

More recently, Weisman and associates[4] described another large, multicenter, double-blind, placebo-controlled trial of the prophylactic use of intravenous immunoglobulin that involved 753 infants. They found that the administration of one dose of immunoglobulin (500 mg/kg of body weight) to preterm neonates delivered at 35 weeks' gestation or before resulted in no difference in the incidence of sepsis, total number of infections, incidence of necrotizing enterocolitis, or death due to sepsis. However, one could argue that the results may be due to the fact that only one dose of immunoglobulin was administered to the participants in this study.

The National Institutes of Health Neonatal Network is now conducting another randomized, controlled trial. Apparently, however, the placebo arm of this trial was eliminated because of some adverse effects observed in participants. Thus, there may be difficulties in the final interpretation of these data as well.

In this issue, the critically designed, expertly carried out, moderate-sized study (n = 170) by Kinney and colleagues is presented.[5] These authors seem to have touched all of the bases in randomly selecting infants of different weights to blindly receive intravenous immunoglobulin (750 mg/kg of body weight) or a placebo. In contrast to the study by Weisman et al,[4] the infants in this trial received repeated doses of immunoglobulin (750 mg/kg of body weight) at 2-week intervals until discharge from the hospital. Even so, the authors found that the intravenous immunoglobulin did not affect the rate of systemic or localized infection. In addition, it did not affect the development of necrotizing enterocolitis, length of hospitalization, or use of antibiotics, assisted ventilation, or supplemental oxygen. Once again, the causes of both systemic and localized infections in patients who received intravenous immunoglobulin or a placebo in this study were not organisms usually associated with invasive neonatal disease, such as group B streptococci, *Escherichia coli* K1, or *Listeria monocytogenes*, but were coagulase-negative staphylococci, *S aureus*, and *Serratia marcescens*. The development of infection with these organisms is usually associated not with specific antibody deficiency but with indwelling catheters, respirators, and other invasive maneuvers so common in neonatal intensive care units. It is unlikely, therefore, that any study of intravenous immunoglobulin that focuses on the prevention of infection caused by these organisms will ever show a truly beneficial prophylactic effect. Furthermore, it may be impossible to design and conduct a study of the prophylactic effects of intravenous immunoglobulin large enough to show a beneficial effect on antibody-dependent, invasive, group B streptococcal, *E coli* K1, or *Listeria* infections given the low attack rate of these infections. An alternate and perhaps more successful strategy may be to employ standard intravenous immunoglobulin[1,6] or human monoclonal or hyperimmune intravenous immunoglobulin preparations[7] to treat, rather than prevent, invasive neonatal infections.

HARRY R. HILL, MD
Departments of Pediatrics and Pathology
University of Utah
50 N Medical Dr
Salt Lake City, UT 84132

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In Other AMA Journals

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Ronald F. Young, MD (*Arch Surg.* 1991;126:1237-1242)

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Markus S. Roessler, MD; David H. Wisner, MD;
James W. Holcroft, MD (*Arch Surg.* 1991;126:1243-1244)

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Steven L. Moulton, MD; Frank P. Lynch, MD;
Timothy G. Canty, MD; David L. Collions, MD; David B. Hoyt, MD
(*Arch Surg.* 1991;126:1262-1266)

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Kenneth Cox, MD; Waldo Concepcion, MD;
William Berquist, MD; Thomas R. Russell, MD
(*Arch Surg.* 1991;126:1278-1286)

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G.U. System: Urinary frequency, difficult urination.

G.I. System: Epigastric discomfort, anorexia, nausea, vomiting, diarrhea, constipation.

Respiratory System: Tightness of chest and wheezing, shortness of breath.

Hematologic System: Hemolytic anemia, thrombocytopenia, agranulocytosis.

Overdosage: ***Signs and Symptoms:*** Central nervous system effects from overdosage of brompheniramine may vary from depression to stimulation, especially in children. Anticholinergic effects may be noted. Toxic doses of pseudoephedrine may result in CNS stimulation, tachycardia, hypertension, and cardiac arrhythmias; signs of CNS depression may occasionally be seen. Dextromethorphan in toxic doses will cause drowsiness, ataxia, nystagmus, opisthotonos, and convulsive seizures.

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Treatment: Induce emesis if patient is alert and is seen prior to 6 hours following ingestion. Precautions against aspiration must be taken, especially in infants and small children. Gastric lavage may be carried out, although in some instances tracheostomy may be necessary prior to lavage. Naloxone hydrochloride 0.005 mg/kg intravenously may be of value in reversing the CNS depression that may occur from an overdose of dextromethorphan. CNS stimulants may counter CNS depression. Should CNS hyperactivity or convulsive seizures occur, intravenous short-acting barbiturates may be indicated. Hypertensive responses and/or tachycardia should be treated appropriately. Oxygen, intravenous fluids, and other supportive measures should be employed as indicated.

Dosage and Administration: Adults and children 12 years of age and over: 2 teaspoonfuls every 4 hours. Children 6 to under 12 years: 1 teaspoonful every 4 hours. Children 2 to under 6 years: 1/2 teaspoonful every 4 hours. Children 6 months to under 2 years: Dosage to be established by physician.

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Efficacy and Pharmacokinetics of Intravenous Immune Globulin Administration to High-Risk Neonates

Janet Kinney, MD; Lucinda Mundorf, RN; Christine Gleason, MD; Carlton Lee, PharmD; Timothy Townsend, MD; Roshelle Thibault, RPh; Anna Nussbaum, MD; Helen Abby, PhD; Robert Yolken, MD

• *Objective.*—To determine whether intravenous immune globulin (IVIG) administration modifies the incidence of infections in high-risk neonates.

***Design.*—Randomized, double-blind study.**

***Setting.*—Neonatal intensive care unit at a tertiary care center.**

***Participants.*—A total of 170 infants were enrolled, 82 of whom received IVIG and 88 of whom received the placebo preparation. Infants were stratified by birth weight into one of three groups (category 1, those weighing less than 1000 g; category 2, those weighing between 1000 and 1500 g; and category 3, those weighing more than 1500 g).**

***Interventions.*—Intravenous immune globulin (750 mg/kg of body weight), or albumin placebo was administered within 72 hours of admission to the tertiary care center and every 14 days thereafter until discharge from the neonatal intensive care unit or age 3 months. Serum IgG levels were measured and data collected relating to the incidence of systemic and localized infections and to the course of hospitalization.**

***Measurements and Main Results.*—The administration of IVIG had no major side effects and resulted in higher serum IgG levels in infants in all birth weight categories compared with infants receiving the placebo. Systemic infections developed in five IVIG-treated infants and five placebo-treated infants. Administration of immunoglobulin had no significant effect on the rate of localized infections or necrotizing enterocolitis. It also did not affect hospital course of the infants as measured by length of hospitalization or the number of days on assisted ventilation, supplemental oxygen, or antibiotics was required.**

***Conclusions.*—The general administration of IVIG using this dosage regimen has limited effects on the clinical course of infants in a neonatal intensive care unit.**

(*AJDC.* 1991;145:1233-1238)

Infants admitted to a neonatal intensive care unit (NICU) are at high risk of infection. Premature infants are susceptible to infection because of many factors, including the relatively low level of immunoglobulins transferred across the placenta before the last month of gestation and the immature function of phagocytic cells.[1-4] Full-term infants in an NICU for an extended period may also be at risk of infections because of a rapid decline in maternally acquired antibodies and other factors related to their hospitalization.[1,5] Recently, preparations have become available that allow the intravenous administration of human immune globulins obtained from large pools of donors. These immune globulin preparations contain antibodies to a wide range of microorganisms that are potentially pathogenic in neonates.[6] However, studies measuring the actual effect of intravenous immune globulin (IVIG) administration on the course of hospitalization of infants in an intensive care setting during an extended period have generated conflicting data.[7-14]

We performed a randomized, double-blind trial to determine whether IVIG could be administered safely to infants and whether IVIG administration modifies the incidence of infections in infants in an NICU setting.

PATIENTS AND METHODS

Newborns admitted to the NICU at The Johns Hopkins Hospital, Baltimore, Md, were eligible for the study if they met the following criteria: (1) age less than 72 hours, (2) no severe metabolic disorders or congenital anomalies, (3) no receipt of immune globulin or blood products before enrollment, and (4) no receipt of blood products or immune globulin preparation by the mother within 2 weeks before delivery. The presence of early-onset sepsis or suspected sepsis did not eliminate an infant from the study. After informed consent was obtained, the study infants were enrolled and stratified by birth weight into three categories: those weighing less than 1000 g (category 1), 1000 to 1500 g (category 2), and more than 1500 g (category 3). Using a block randomization technique, infants in each birth weight

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From the Eudowood Division of Infectious Diseases, Department of Pediatrics (Drs Kinney, Townsend, and Yolken and Ms Mundorf), Division of Neonatology, Department of Pediatrics (Dr Gleason), and the Department of Radiology (Dr Nussbaum), The Johns Hopkins School of Medicine; Department of Pharmacy Services, The Johns Hopkins Hospital (Dr Lee and Ms Thibault); and the Department of Biostatistics, The Johns Hopkins School of Hygiene and Public Health, Baltimore, Md (Dr Abby). Dr Townsend is now with the Divisions of Neonatology and Infectious Diseases, The Children's Mercy Hospital, University of Missouri, Kansas City School of Medicine.

Reprints not available.

stratum were assigned to receive either IVIG or placebo. Only the pharmacists knew of the infants' assignments to the IVIG or placebo group. This study was approved by the Joint Committee on Clinical Investigation of The Johns Hopkins Medical Institutions. It was overseen by an independent monitoring committee that confirmed the case definitions and determined the study end points.

An intravenous immune globulin, Gamimune-N (5% human immunoglobulin in 10% maltose [pH 4.5]) or placebo (0.1% albumin in 10% maltose) was administered intravenously to the infants within 72 hours of admission and every 14 days thereafter until discharge from the NICU or age 3 months. The IVIG was administered at a dose of 750 mg/kg of body weight, and placebo was prepared to be administered in a solution that had the same volume and appearance as the IVIG. Doses of IVIG and placebo were administered slowly using a syringe pump at an initial rate of 1 mL/kg of body weight per hour.

Detailed pharmacokinetic studies were performed involving selected infants enrolled in each weight category who received IVIG or placebo. Serum samples were obtained immediately before each infusion and 2, 3, and 7 days after infusion for up to three transfusions. In addition, cord blood samples were analyzed when available. The samples were analyzed using nephelometric methods to ascertain IgG concentration. The elimination (β) half-life was calculated using regression analysis (natural logarithm vs time). The volume of distribution was calculated using the noncompartmental model.[15]

Total IgG levels were also measured in each study infant before each infusion so that the preinfusion level of IgG could be ascertained. Preinfusion values were obtained for up to six infusions, and detailed time points were obtained for up to three infusions per infant. Levels were measured only while the infants were in the NICU.

Vital signs were monitored during infusions, and any adverse reaction or notable alteration in clinical status that occurred during or within 48 hours of the infusion was recorded. Levels of serum glucose were measured immediately before and 48 hours after the infusion using glucose oxidase strips (Chemstrips, Miles Laboratories, Elkhart, Ind). Oxygen saturation was monitored during the infusions using pulse oximetry. Gestational maturity was determined with clinical parameters using standard methods.[16]

Each episode of bacterial infection was recorded and categorized as systemic or localized. Systemic bacterial infections were defined when blood or cerebrospinal fluid cultures were positive for defined bacterial agents. The clinical significance of a blood culture positive for *Staphylococcus epidermidis* and other strains of staphylococci that do not produce coagulase is difficult to interpret with certainty in this patient population.[17,18] For this reason, a neonatologist and an infectious diseases attending physician not participating in the study and unaware of the treatment assignments reviewed each case in which a blood culture positive for coagulase-negative staphylococci was obtained. They considered an infant to have undergone systemic infection with coagulase-negative staphylococci if (1) the infant displayed signs and symptoms of sepsis and had two blood cultures positive for coagulase-negative staphylococci from at least two different blood sampling sites (including a central line) or from different days, or (2) the infant displayed signs and symptoms of sepsis, and one blood culture yielded pure coagulase-negative staphylococci within 24 hours of inoculation. Infants who had cultures positive for coagulase-negative staphylococci but who did not meet these criteria were not considered to have undergone systemic infection with coagulase-negative staphylococci. In addition, cultures positive for nonbacterial organisms such as *Candida albicans* were not included in the analysis of systemic bacterial infections.

Localized bacterial infections analyzed included tracheitis, urinary tract infections, wound infections, and conjunctivitis. Tracheitis was defined as the presence of purulent tracheal secretions coincident with the cultivation of a potential pathogen from endotracheal secretions associated with respirator deterioration. A urinary tract infection was defined as th presence of more than 10 000 organisms on culture of a urin specimen obtained using a catheter or suprapubic puncture A wound infection was characterized as the presence of purulent discharge from a break in the skin and yielding of microorganism from culture of the discharge. Conjunctiviti was defined as the presence of purulent discharge from th eye associated with the cultivation of a bacterial pathogen. I each case, an episode of localized infection was considered separate event if it occurred at least 1 week before or afte another episode involving the same mucosal surface. We di not attempt to systematically identify viral or fungal organisms in this study.

The infants were also evaluated to detect gastrointestina disease, which was divided into three categories: necrotizin enterocolitis (NEC), suspected NEC, and gastroenteritis. Necrotizing enterocolitis and suspected NEC were defined according to the criteria of Bell et al.[19] Gastroenteritis was defined as an illness characterized by the passage of more than two loose, watery stools during two consecutive 8-hour periods or the passage of more than four loose, watery stools during 24 hours.[5]

In addition to the above determinations, we measured the number of days during which an antibiotic was administered to the infant after enrollment in the study, regardless of the culture results. We also determined the number of days during which an infant required assisted ventilation with a mechanical ventilator or continuous positive airway pressure device and the number of days during which an infant was administered supplemental oxygen using a face mask, nasal cannula, or hood in the absence of assisted ventilation. For these analyses, a day was recorded if the indicated therapy was administered at any time during 24 hours. The presence of intracranial hemorrhage was determined using ultrasound evaluations obtained during the first, second, and sixth weeks of life for infants born at less than 32 weeks' gestation and when clinically indicated for other infants.

The study was overseen by a study monitoring committee that included a neonatalogist, infectious disease specialist, and a statistician not participating in the study. The committee periodically reviewed the efficacy data and made decisions concerning the inclusion of cases of infection and the length of the study. The committee decided to terminate the study when they determined that a statistically significant difference in rates of infection could not be achieved in a reasonable period of time.

Statistical analyses were performed with the CSS Statistical Package (Statsoft Inc, San Francisco, Calif).

RESULTS

Study Population

Between May 1987 and April 1989, 187 infants were enrolled in the study. A total of 17 of the 187 infants originally enrolled were eliminated from the analysis for any of the following reasons: (1) infant was in the NICU less than 48 hours (n = 14); (2) infant received an exchange transfusion (n = 1); and (3) infant received the wrong study drug owing to pharmacy error (n = 2). Therefore, 170 infants completed the study. Of the 88 infants who received IVIG, 25 were in birth weight category 1; 29, category II; and 34, category 3. The birth weight distribution of the 82 infants receiving placebo was 24, 30, and 28 for categories 1, 2, and 3, respectively.

The demographic characteristics of participants in both groups were similar (Table 1). There were no statistically significant differences between the IVIG and placebo groups as a whole or within the birth weight groups for sex, race, type of delivery, gestational maturity, or mul-

Table 1.—Demographic Characteristics of Study Population*

	No. (%) of Patients Receiving Immune Globulin	No. (%) of Patients Receiving a Placebo
Infant Characteristics		
Male	44 (50)	43 (51)
White	32 (36)	38 (45)
SVD	43 (51)	38 (45)
AGA	71 (81)	70 (83)
Multiple gestation	16 (18)	15 (18)
Maternal history before delivery		
Hypertension	14 (16)	9 (11)
Preeclampsia	14 (16)	9 (11)
Intrapartum fever	27 (31)	22 (26)
Premature ROM	43 (49)	51 (61)
Prolonged ROM	35 (40)	39 (35)

*$P>.1$ by χ^2 analysis for all demographic characteristics and administration of intravenous immune globulin or a placebo. SVD indicates spontaneous vaginal delivery; AGA, appropriate for gestational age; and ROM, rupture of membranes.

tiple gestation. There were also no differences between treatment groups for mean birth weight and Apgar scores. The distribution of maternal risk factors such as hypertension, preeclampsia, intrapartum fever, prematurity, and prolonged rupture of membranes was similar in the two treatment groups.

A total of 474 infusions were administered to 170 study infants as follows: 235 infusions to 88 infants in the IVIG group and 239 infusions to 82 infants in the placebo group. The mean number of infusions was 2.67 per infant in the IVIG group and 2.91 per infant in the placebo group. In category 1, an average of 4.44 infusions were administered per child in the placebo group and 4.45 infusions per child in the group receiving IVIG. No life-threatening reactions were noted to have been associated with the infusion of the IVIG or placebo preparations. Alteration in clinical status occurred several times during infusion and within 48 hours after infusion. These alterations included minor changes in respiratory, cardiac, and gastrointestinal function (Table 2). However, the frequency of these events in the infants receiving IVIG did not differ from that of the infants receiving placebo ($P>.2$ by Fisher's Exact Test for all comparisons). One infant who received IVIG developed a fever (38.5°C) after the fifth infusion and was not administered additional doses of the study drug. On retrospective review of the patient's chart, the fever was not believed to be attributable to IVIG. None of the other alterations in clinical status were judged to be of sufficient severity to warrant the withholding of subsequent infusions.

Pharmacokinetics

Serial IgG levels were measured 2, 3, 7, and 14 days after infusion in 35 of the infants who received IVIG. A total of 19 of these infants were in birth weight category 1, 10 infants were in birth weight category 2, and six were in birth weight category 3. Only infants from whom a complete set of blood specimens was obtained were included in the analysis. Data were obtained from up to three infusions per infant. The smaller number of infants studied in the higher birth weight categories is a reflection of their shorter length of stay in the NICU and of the fact that several of the infants enrolled were discharged before 14 days after infusion.

The mean preinfusion (trough) IgG levels for each weight category are depicted in Fig 1. Mean levels of IgG measured at birth or immediately before the first infusion were not different between IVIG and placebo groups. After administration of the study drug, mean IgG levels obtained before each subsequent dose were significantly higher in IVIG-treated neonates than in the infants receiving the placebo preparations for all birth weight groups ($P<.05$ by the Mann-Whitney *U* Test for all comparisons). The serum half-life of IVIG in the study infants was 18.1 days (95% confidence interval, 15.5 to 20.6 days). The volume of distribution of the IVIG was 0.082 L/kg of body weight (95% confidence interval, 0.074 to 0.090 L/kg). There were no statistically significant differences in serum half-life or volume of distribution among the birth weight categories. The mean levels of IgG during the 14 days after infusion are depicted in Fig 2.

Infections

Ten systemic bacterial infections were documented in 10 different infants evaluated during the study. Five of the episodes of systemic bacterial infection occurred in infants receiving IVIG, while five occurred in infants who received the placebo preparation. The difference in observed infection rates between the treatment groups was 0.4% (95% confidence interval, −6.7% to +7.5%). The five systemic infections in the infants receiving IVIG were detected using samples obtained on days 2, 5, 6, 9, and 13 after infusion. The five infections in the infants in the placebo group were detected on days 3, 5, 6, 9, and 14 after infusion.

Systemic infections in the infants receiving IVIG were caused by *Staphylococcus aureus* (n = 2), coagulase-negative staphylococci, *Escherichia coli*, and *Serratia marcescens*. Systemic bacterial infections in the neonates receiving placebo included coagulase-negative staphylococci (n = 2), *S aureus*, *S marcescens*, and *Enterobacter gergoviae*. Six of the 10 systemic bacterial infections occurred in infants with birth weights of less than 1000 g. These infections were also equally divided between the IVIG and placebo groups.

A total of 19 episodes of localized bacterial infection, as defined above, occurred in 17 infants during the study. Eleven of the localized infections occurred in 10 infants who had received IVIG, while eight localized infections were observed in seven infants who had received placebo. The sites of infection are enumerated in Table 3. The infections were caused by a wide range of microorganisms, including *S aureus*, coagulase-negative staphylococci, *Streptococcus faecalis*, *E coli*, *Moraxella catarrhalis*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *S marcescens*, and *Acinetobacter baumannii* (formerly *A calcoaceticus*, biovar *anitratus*).

There were three cases of definite NEC and seven cases of suspected NEC. Four infants had gastroenteritis, as defined above, without signs of symptoms of NEC (Table 3). Thus, six infants with gastrointestinal symptoms had received IVIG and eight had not.

We also examined the effect of IVIG on the course of hospitalization of the infants (Table 4). Infants receiving IVIG were hospitalized for a mean of 43.1 days, while

Table 2.—Reactions Temporally Associated With Infusions of Intravenous Immune Globulin or a Placebo

	Birth Weight <1000 g		All Birth Weights	
	Intravenous Immune Globulin	Placebo	Intravenous Immune Globulin	Placebo
No. of infusions	111	107	225	239
No. of reactions				
Acidosis (pH<7.3)	7	2	9	3
Apnea	2	4	2	9
Tachypnea (>40 breaths/min)	5	1	5	1
Oxygen desaturation (<90%)	10	5	15	11
Fever (>38.5°C)	1	0	1	0
Lethargy	1	2	2	3
Tachycardia (>120 beats/min)	7	2	7	6
Bradycardia (<60 beats/min)	4	7	7	13
Emesis	2	2	2	5
Abdominal distention (>1 cm)	1	0	1	0
Hyperglycemia (>6.6 mmol/L [>120 mg/dL])	6	10	8	13
Hypoglycemia (<2.2 mmol/L [<40 mg/dL])	12	10	21	18

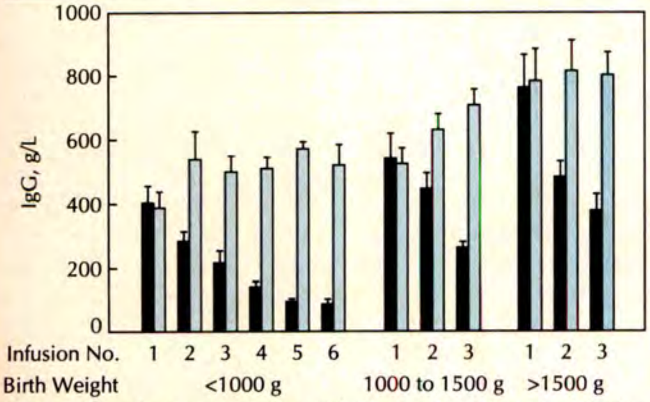

Fig 1.—*Trough serum immune globulin levels. The serum IgG levels were measured in all study infants before each infusion. The infusions were administered every 14 days while the infants were participating in the study. Values indicate the mean±95% confidence interval of the IgG levels measured in infants in the indicated birth weight strata. Solid bars indicate infants who received intravenous immune globulin (IVIG), and shaded bars, infants who received placebo. Numbers on the x axis indicate the infusion number before which the corresponding level was measured. Note that values for infusions 2 through 6 were obtained before the administration of IVIG or placebo.*

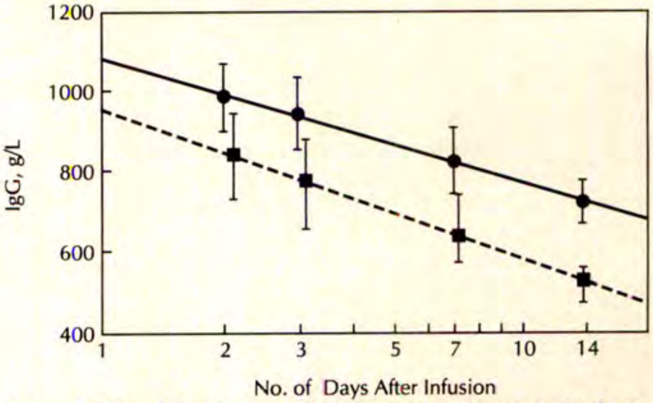

Fig 2.—*IgG levels in intravenous immune globulin–treated infants. Values are geometric means±95% confidence intervals of the IgG levels at the indicated times after infusion. Lines indicate the log-linear regression of the levels for infants weighing less than 1000 g at birth (squares; n=19) and infants weighing 1000 g or more at birth (circles; n=16). Values for up to three infusions were used for these analyses.*

those receiving placebo were hospitalized for a mean of 46.5 days ($P>.2$ by the Mann-Whitney *U* Test). Infants in the IVIG group received antibiotics for a mean of 9.4 days, while those in the placebo group received antibiotics for a mean of 9.2 days ($P>.5$ by the Mann-Whitney *U* Test). There were also no differences in the total number of days during which infants required supplemental oxygen therapy or assisted ventilation. Five infants in the IVIG group had evidence of intracranial hemorrhage as documented with cranial ultrasound examinations. Four of these cases were judged to be grade 3 or grade 4 hemorrhages. Seven patients receiving placebo had intracranial hemorrhage, and five of these were grade 3 or grade 4 hemorrhages.

Eight infants died during the study. Of these, four had received IVIG and four, placebo. Three of the deaths were directly associated with infection. Two of the infection-related mortalities occurred in the placebo group—one in an infant with staphylococcal-scalded skin syndrome and bacteremia due to *S aureus* and another in an infant with severe NEC and bacteremia with *E gergoviae*. The third infection-related death occurred in an infant who had received IVIG and who had bacteremia with *S marcescens*.

COMMENT

Our study indicates that IVIG can be administered safely to infants in an NICU and that IVIG administration results in higher levels of serum IgG. The pharmacokinetics in our IVIG-treated infants were similar to those reported by others.[20]

The administration of IVIG in a controlled, double-blinded fashion did not result in a decrease in the rate of systemic or localized microbial infection. We noted an incidence of systemic bacterial infection of 5.9% (ten of 170) among all study infants and of 12.2% (six of 49) among category 1 infants. Five infants in both the IVIG-treated group and the control group had culture-proven, systemic, bacterial infection. Eleven of the

Table 3.—Number of Episodes of Infection and Other Conditions Occurring in Neonates Receiving Intravenous Immune Globulin or a Placebo

	Patient Receiving Intravenous Immune Globulin (n=88)	Patients Receiving a Placebo (n=82)
Infections		
Systemic	5	5
Local	11	8
Tracheitis	4	4
Wound	3	0
Urinary	4	3
Eye	0	1
Total	**16**	**13**
Gastrointestinal conditions		
Definite necrotizing enterocolitis	1	2
Suspected necrotizing enterocolitis	3	4
Gastroenteritis	2	2
Total	**6**	**8**
Total	**22**	**21**

Table 4.—Effect of Intravenous Immune Globulin on Course of Hospitalization of High-Risk Neonates*

	Patients Receiving Intravenous Immune Globulin	Patients Receiving a Placebo
Hospital stay		
No.	88 (100)	82 (100)
Mean	43.1 (36.3-49.9)	46.5 (39.0-54.0)
Antibiotics		
No.	76 (86.4)	75 (91.5)
Mean	9.4 (7.7-11.1)	9.2 (7.2-11.1)
Assisted ventilation†		
No.	66 (75.0)	60 (73.2)
Mean	12.7 (8.7-16.7)	15.5 (10.0-21.0)
Supplemental oxygen‡		
No.	53 (60.2)	50 (61.0)
Mean	16.5 (10.7-22.4)	14.2 (9.4-19.0)

*Data are number (percent) of patients in the indicated category and the mean (95% confidence interval) of the infants in the category.

†Includes infants treated with mechanical ventilators or continuous positive airway pressure.

‡Includes infants not receiving assisted ventilation but receiving supplemental oxygen via nasal cannula, face mask, or hood.

IVIG-treated infants and eight infants in the placebo group developed local infections. There was no statistical difference between groups in the development of gastrointestinal illness, including NEC. In essence, we found that the administration of IVIG had no significant effect on the rate of systemic infection, localized infection, or NEC.

It is of note that the infants in our study population did not develop infections with organisms widely recognized as pathogens in neonates, such as group B streptococcus, enteric gram-negative rods or *Listeria monocytogenes*. Rather, the infecting microflora represented organisms commonly encountered in nosocomial infections in other inpatient intensive care populations, including a high rate of staphylococcal infections. The increased survival of high-risk infants results in long-term stays in intensive care settings and, subsequently, increased exposure to microflora and other environmental conditions that can lead to nosocomial infections.

The detection of infectious processes is a problem when studying any neonatal infection. While the identification of a pathogenic organism from a normally sterile body site, such as blood or cerebrospinal fluid, is a specific sign of infection, it is likely that microbiologic cultivation techniques do not detect all episodes of neonatal infection. This limitation is particularly a problem among low-birth-weight infants because repeated samples of large volumes of blood generally cannot be obtained. The frequent use of antibiotics in this population may also affect the rate of recovery of pathogenic microorganisms. Also, such methods will not detect anaerobic organisms and infections with nonbacterial agents, such as viruses or genital mycoplasmas.[21] It is possible that IVIG was affecting infectious processes in a way not evident from the analysis of blood cultures.

For this reason, we also examined the effect of IVIG on other parameters that might be related to infectious processes occurring in the study infants. We could find no effect of IVIG administration on the rate of localized bacterial infections, nor could we document an effect of IVIG on the incidence of NEC or other forms of gastrointestinal illness. Similarly, the administration of IVIG did not alter the number of days during which the infant was administered antibiotics by the attending physician. In addition, the administration of IVIG did not affect the length of hospitalization or the number of days in which assisted ventilation was required or supplemental oxygen was administered. Thus, we found no evidence that the administration of IVIG affected parameters that might be related to the occurrence of systemic or localized infectious processes.

Previous studies have presented contradictory findings concerning the effect of IVIG on the rate of infection in the NICU population. Some studies document a decrease in systemic infections,[8,9,12,14] while other studies show no significant affect on infection rate.[13] These differences might relate to the dosing regimens, constitution of the IVIG preparations, sample size, definition of infectious processes, or the incidence of the infections in the study populations. It is possible that the administration of IVIG at a higher dose or more frequent dosing interval or maintenance of a targeted level of IgG[22] would have more greatly affected the incidence of systemic infections. Likewise, a reduction in the incidence of infection might be observed in a population with a much higher incidence of infection or NEC.[8,9,12]

In essence, results of our study indicate that it is unlikely that the general administration of IVIG to neonates in an NICU setting with relatively low rates of infection will result in a substantial alteration in hospital course. In light of the cost of IVIG preparations, the routine administration of IVIG to all neonates in intensive care units cannot be recommended at this time. Additional efforts should be directed at the development of more specific therapies for the prevention of infectious complications in high-risk infants.

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Article

Vertical Transmission of Human Immunodeficiency Virus From Seronegative or Indeterminate Mothers

John P. Johnson, MD; Peter E. Vink, MD; Susan E. Hines, MS, C PNP; Barbara Robinson, RNC; John C. Davis, Jr, MD; Prasanna Nair, MD

• *Objective.*—To describe the identification of human immunodeficiency virus (HIV)–infected infants born to women who were seronegative or indeterminate during pregnancy.

***Research Design.*—Longitudinal cohort study.**

***Setting.*—Inner-city medical center.**

***Participants.*—A series of children born to women with histories of risk factors for HIV infection were followed up for studies of the natural history of HIV-infected infants. These children were identified through risk factor assessment of pregnant women presenting for obstetric care.**

***Interventions.*—Counseling and testing to detect HIV.**

***Results.*—Three women were retrospectively identified who were infected with HIV during pregnancy but whose test results showed them to be either seronegative or indeterminate. Two of these women transmitted HIV infection to their children. Subsequently, all three women were confirmed to be infected.**

***Conclusions.*—Standard serologic testing to detect HIV infection will not identify all infected pregnant women. Perinatal transmission of HIV can occur in women with negative results of enzyme-linked immunosorbent assay or indeterminate results of Western blot analysis during pregnancy.**

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In 1983, the first cases of acquired immunodeficiency syndrome in infants were presented.[1,2] Since then, the total number of cases of acquired immunodeficiency syndrome in the pediatric population has grown rapidly to more than 1300.[3] For each case of acquired immunodeficiency syndrome among children, many more children are infected with human immunodeficiency virus (HIV) but have mild or no apparent disease.[4-6] Because most cases of HIV infection in children have resulted from vertical transmission,[7] the Centers for Disease Control and the American College of Obstetrics have recommended the establishment of screening programs for women of childbearing age with risk factors for HIV infection.[8] These programs permit the counseling of women regarding HIV infection and pregnancy and the prospective identification of infants with perinatal exposure to HIV.[9]

Recent evidence suggests that not all infected women will be identified with HIV testing because the sensitivity of enzyme-linked immunosorbent assay (ELISA) testing in some at-risk individuals may be low. These individuals do not demonstrate seroconversion within the usual time, which has been ascribed to a long latency period after infection.[10] The transmission of HIV from seronegative or indeterminate persons by methods other than blood transfusion has not been previously demonstrated.[11] We discuss vertical transmission of HIV to infants born to women with risk factors for HIV infection who had negative or indeterminate responses to serologic tests to detect HIV.

PATIENT REPORTS

PATIENT 1.—A 36-year-old woman presented to the University of Maryland Obstetrical Clinic for prenatal care at 6 months' gestation. At that time, she was enrolled in a methadone maintenance program and admitted to a 10-year history of intravenous heroine and cocaine use. She complained of persistent nonproductive cough, night sweats, odynophagia, myalgias, and arthralgias. Results of physical examination revealed a thin woman with an enlarged, tender liver, a fundal height of 24 cm, white oral plaques, and esophageal erythema consistent with oral and possibly esophageal candidiasis. After written, informed consent was acquired, serum was obtained for HIV testing. Anti-HIV antibody determination by ELISA (DuPont, Wilmington, Del) revealed an OD_{405} value of 0.206, with the positive cutoff value being greater than 0.400.

She presented 6 weeks later in active labor with spontaneous rupture of membranes a few hours earlier. Her gestation was assessed to be $36\frac{4}{7}$ weeks by dates and $26\frac{6}{7}$ weeks by fundal height. Labor was uncomplicated and a female infant was vaginally delivered 3 hours later. Results of antibody ELISA were again negative, with a quantitative value of 0.107 and a positive cutoff value of 0.451.

Results of assessments during the infant's first year revealed episodes of oral and cutaneous candidiasis, atopic dermatitis, otitis media, delayed development, viral pneumonitis, *Staphylococcus epidermidis* septicemia, and hand-foot-and-mouth disease. At age 6 months, a coculture of the child's peripheral blood lymphocytes with donor lymphocytes revealed HIV antigen within 1 week. Attempts to locate the biologic mother of this child after delivery for confirmation of her virologic status were unsuccessful.

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From the Department of Pediatrics, University of Maryland School of Medicine, Baltimore.

Reprint requests to the Division of Pediatric Immunology, School of Medicine, University of Maryland at Baltimore, 655 W Baltimore St, BRB, 10-027, Baltimore, MD 21201 (Dr Johnson).

PATIENT 2.—This patient presented to the University of Maryland Obstetric Clinic at 27 weeks' gestation. She admitted to sexual intercourse with a drug user and a history of multiple sexually transmitted diseases (gonorrhea and syphilis). Results of her physical examination were unremarkable except for a fundal height of 27 cm consistent with normal intrauterine pregnancy. Results of HIV ELISA were positive, while results of Western blot analysis were indeterminate. A second specimen was sent for analysis 2 weeks later and produced the same results. A third specimen, sent to the Red Cross 1 week after the second specimen, showed the patient to be positive by ELISA, while results of Western blot analysis showed her to be negative for HIV.

She presented 3 months later at term, with spontaneous onset of labor, and delivered a healthy male infant weighing 2940 g. Because of the difficulty in determining her serologic status (as recalled by the obstetric staff at that time), HIV testing was repeated. Results of both ELISA and Western blot analysis at this time showed her to be HIV positive; p24 antigen could not be detected in this specimen (HIV-1 p24 Core Profile ELISA DuPont, Boston, Mass). At age 15 months, the child was in good health and had no evidence of HIV infection.

PATIENT 3.—A 26-year-old woman presented to the obstetric clinic with intrauterine pregnancy of approximately 12 weeks' gestation. The patient admitted to intravenous drug use and sexual intercourse with intravenous drug users. Results of physical examination were unremarkable except for fundal height of 11 cm consistent with a 12-week intrauterine pregnancy. Results of HIV ELISA were positive, while results of Western blot analysis were indeterminate. An indeterminate result of the Western blot analysis was confirmed by the Maryland State Health Department. Four months later, ELISA was again performed and the results were positive. Results of another Western blot analysis showed the patient to be negative for HIV.

A vaginal delivery at 40 weeks' gestation produced a 2580-g, well-appearing female. At age 4 months, the child was noted to have hepatomegaly, splenomegaly, and an eczematoid skin rash. At ages 4 and 6 months, she was documented to have p24 serum antigenemia, with levels of 214 and 250 pg/mL, respectively.

In view of the findings in the child at age 6 months, the mother was reevaluated and confirmed at that time to be HIV seropositive by results of both ELISA and Western blot analysis. A serum specimen that had been collected and frozen at delivery was assayed and found to have 5.14 pg of p24 serum antigenemia per milliliter.

COMMENT

This report documents the retrospective identification of HIV infection in three pregnant women. Results of tests to detect HIV were indeterminate in two of the women, while the other woman was seronegative. Of even greater concern is that two of these women transmitted HIV to their children. Several explanations might account for the lack of confirmed seropositivity in these infected pregnant women: (1) the "window" period that follows infection with HIV and precedes seroconversion; (2) seroreversion, ie, the loss of HIV antibodies (this is usually seen in late symptomatic HIV infection, but has been described in asymptomatic individuals)[12]; (3) false-negative results of an antibody test; and (4) human error.

The window period of HIV infection is the time between exposure resulting in infection and the presence of detectable anti-HIV antibody. In approximately 95% of infected individuals, anti-HIV antibody is detectable within 6 months.[13] Patients 2 and 3 experienced complete seroconversion within 3 and 7 months of initial identification, respectively. Prolonged window periods lasting longer than 6 months were first reported in 1987.[10] Imagawa and colleagues[14] have prospectively described 31 (23%) of 133 men involved in high-risk activity who remained seronegative for up to 36 months after positive results of a culture to detect HIV. Wolinsky and colleagues[15] have prospectively shown a median of 18 months from positive results of polymerase chain reaction assay to Western blot analysis confirming the presence of HIV in 24 individuals and up to 42 months in two individuals. Latency has been suggested to explain why some individuals have such low titer antibody responses as to be undetectable. This phenomenon has been documented only in homosexual men, but it is reasonable to assume a similar phenomenon may occur in heterosexuals with risk factors for HIV related to intravenous drug use. Whether latency is more likely in pregnancy remains to be evaluated.

Patient 1 had physical findings suggestive of advanced disease, ie, oral and possibly esophageal candidiasis. The poor outcome of her pregnancy further suggests her ill health. Advanced disease has been associated with the loss of specific anti-HIV seroreactivity, ie, seroreversion. The loss of maternal anti-HIV antibody may permit the transmission of the virus, as has been demonstrated in other intrauterine infections with such viruses as varicella-zoster and rubella. The importance of anti-HIV antibody response has recently been demonstrated by the correlation of vertical transmission with an absence of maternal antibody against gp120.[16,17] Thus, seroreversion may increase the risk of vertical transmission.

Finally, human error and the test validity of Western blot analyses (which are often difficult to interpret) may be other mediating factors in the identification of HIV infection. Results of a survey of laboratories participating with the College of American Pathologists in performing Western blot analysis revealed only an 89.2% rate of correct identification of positive specimens. In another study by the Department of Defense comparing the performance of Western blot analysis in 19 laboratories, 10 laboratories failed the required proficiency panel at least once. Thus, there is still a lack of standardization in performing Western blot analyses and evaluating their results.[18,19]

The frequency of vertical HIV transmission from at-risk women shown to be HIV seronegative or indeterminate to their infants is uncertain. Long-term follow-up of both maternal and pediatric populations will be necessary to determine this. The identification of three such cases during 2 years from one program raises concern about ascertainment of HIV infection in pregnant, at-risk women. These cases suggest that, in women with histories or physical findings suggestive of HIV infection, a negative or indeterminate test result should be followed by a repeated test and/or other assays to detect infection (eg, peripheral blood coculture, polymerase chain reaction assay, or p24 antigen capture assay). It is remarkable that approximately half of the latently infected seronegative persons in the study by Ranki et al[10] were positive for p24 antigen.

It is certain that vertical transmission of HIV from at-risk women with seronegative or indeterminate results of anti-HIV antibody tests will occur, that obstetricians and pediatricians must be aware of maternal risk factors in addition to maternal serologic status, that women with risk factors should be tested several times during pregnancy (and with several assays), and that children born to seronegative, at-risk women should also be regarded as at risk for HIV infection.

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CORRECTION

Incorrect Notations and Incomplete Footnote.— In the article titled "Evaluation of Intraosseous vs Intravenous Antibiotic Levels in a Porcine Model," published in the August issue of *AJDC* (1991;145:946-949), errors were made in the table and its footnote. On page 947, throughout the table, under the "Drug" column, the following notations should have been published C_{max} and T_{max}. The footnote for the Table was incomplete. It should have read as follows: "*Values are mean±SD. AUC indicates area under the plasma concentration time curve; C_{max}, maximum concentration; T_{max}, the time to peak plasma concentration; and NS, not significant."

Child Survival and Perinatal Infections With Human Immunodeficiency Virus

John V. Bennett, MD, Martha F. Rogers, MD

• A mathematical model was developed to assess the effect of various assumed prevalence rates of maternal human immunodeficiency virus (HIV) infection on perinatally acquired HIV infections and child survival. The model indicates that for children younger than 5 years, countries with low baseline mortality rates will experience greater relative increases in child mortality rates and larger proportions of HIV-caused deaths in children than countries with high mortality rates. It also suggests that perinatal HIV infection could become the most common cause of deaths in children in the developed world if maternal infection rates reach 2% to 3%. Rates of 25% to 30% would be needed to produce a similar effect in the developing world. Child survival gains in the last three decades in the developed world could be quickly erased at low levels of maternal HIV infection, but gains would not be completely offset in the developing world until more than 40% of mothers became infected with HIV. When basic demographic information and the maternal HIV infection rate are known, the model permits a direct assessment of infant and child mortality caused by HIV. It can also be used to estimate the prevalence of maternal HIV infection when values for all other variables are known.

(*AJDC*. 1991;145:1242-1247)

Over the past decade, human immunodeficiency virus (HIV) infection has spread throughout the world; over 150 countries have now reported cases to the World Health Organization. In the United States, Europe, and other developed countries, most women have become infected either through the abuse of intravenous drugs or by sexual contact with men who became infected through intravenous drug abuse. Women and children in these countries represent approximately 10% and 2%, respectively, of acquired immunodeficiency syndrome (AIDS) cases (World Health Organization Collaborating Centers). The overall seroprevalence of HIV among women in most developed countries is less than 1%,[1-3] but has exceeded 50% in subpopulations of intravenous drug-abusing women.[4] By contrast, in the developing countries of sub-Saharan Africa and the Caribbean, HIV has spread to women primarily through heterosexual contact, and the male-female ratio among infected persons is approximately 1:1.[5] The seroprevalence among pregnant women in some urban areas of these countries has exceeded 20%.[6]

Children acquire HIV infection primarily through perinatal exposure to their infected mothers. Between 20% and 40% of infants born to infected mothers appear to acquire HIV infection from their mothers[7-9]; one recent study reported a rate of 13%.[10] Many infected infants die in the first year of life as a consequence of this infection, and most are considered likely to succumb before their fifth birthday.[7-11] Early HIV-caused deaths are likely to occur more commonly among infected children in developing countries, where malnutrition and pulmonary and other infections are more likely, preventive measures such as immunoglobulin prophylaxis and zidovudine treatment are not available, and clinical treatment of illnesses is not optimal.

We selected infant and child mortality rates (MRs), as tallied by the United Nations Children's Fund in 1987,[12] for the baseline rates of 131 major countries of the world. We then sought to quantitate the effect of various assumed levels of maternal HIV infection on child survival. To do this, we used a mathematical model based on births, mother-to-infant transmission rates, and MRs for infants (defined as children between birth and age 1 year), 1- to 5-year-olds, and children younger than 5 years. Mortality rates were estimated for infants with and without HIV infection. This approach enabled us to compare the impact on childhood MRs in developing and developed countries with high and low baseline mortality rates, and to examine the potential for offsetting gains in child survival since 1960.

MATERIALS AND METHODS

Methods

Data and assumptions used in the mathematical model are detailed below and summarized in Table 1. To describe a country's MR for its children younger than 5 years, we used the following terms as defined by the United Nations Children's Fund: *very high, high, medium,* or *low.*

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From The Task Force for Child Survival and Development, The Carter Center, Atlanta, Ga (Dr Bennett); Emory University School of Public Health, Atlanta (Dr Bennett); and the Division of Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome, Center for Infectious Diseases, Centers for Disease Control, Atlanta (Dr Rogers).

Reprint requests to The Task Force for Child Survival and Development, The Carter Center, One Copenhill, Atlanta, GA 30307 (Dr Bennett).

Table 1.—Variables Used in Perinatal HIV Infection Model*

UNICEF Classification of MR for Children Under 5 Years Old (Deaths per 1000 Live Births)	No. of Countries	Median MR		Mother-to-Child Transmission Rate, %	% of HIV-Infected Infants Dying of All Causes by Age	
		Children<5 y Old	Infants		1 y	5 y
Very high (over 170)	33	209	129	40	50	85
High (95-170)	30	123	84	40	40	75
Medium (31-94)	29	60	45	30	25	60
Low (under 30)	39	13	10	30	15	50

*UNICEF indicates United Nations Children's Fund; MR, mortality rate; and HIV, human immunodeficiency virus. All rates apply to 1000 live births. The *Very High* group includes Afghanistan, Mali, Mozambique, Angola, Sierra Leone, Malawi, Ethiopia, Guinea, Burkina Faso, Niger, Chad, Guinea-Bissau, Central African Republic, Somalia, Mauritania, Senegal, Rwanda, Kampuchea, People's Democratic Republic of Yemen, Bhutan, Nepal, Yemen, Burundi, Bangladesh, Benin, Madagascar, Sudan, United Republic of Tanzania, Nigeria, Bolivia, Haiti, Gabon, and Uganda; the *High* group, Pakistan, Zaire, Laos, Togo, Cameroon, India, Liberia, Ghana, Oman, Côte d'Ivoire, Lesotho, Zambia, Egypt, Peru, Libyan Arab Jamahiriya, Morocco, Indonesia, Congo, Kenya, Zimbabwe, Algeria, Honduras, Guatemala, Saudi Arabia, Nicaragua, Burma, South Africa, Turkey, Iraq, and Botswana; the *Medium* group, Islamic Republic of Iran, Vietnam, Ecuador, Brazil, El Salvador, Tunisia, Papua New Guinea, Dominican Republic, Philippines, Mexico, Colombia, Syrian Arab Republic, Paraguay, Mongolia, Jordan, Lebanon, Thailand, Albania, China, Sri Lanka, Venezuela, Guyana, Argentina, Panama, Democratic Republic of Korea, Republic of Korea, Malaysia, United Arab Emirates, and Uruguay; and the *Low* group, USSR, Mauritius, Romania, Yugoslavia, Chile, Trinidad and Tobago, Kuwait, Jamaica, Costa Rica, Bulgaria, Poland, Cuba, Hungary, Portugal, Greece, Czechoslovakia, Belgium, United States, New Zealand, Israel, Austria, Singapore, Italy, United Kingdom, Ireland, Germany, Denmark, Spain, Australia, France, Hong Kong, Canada, the Netherlands, Norway, Switzerland, Japan, Finland, and Sweden.

Information on perinatal HIV infections from the developing world is limited. A prospective study from 1987 to 1989 on mothers and newborns in Haiti, a country with a very high MR for children younger than 5 years in 1987,[12] showed HIV seropositivity in 443 (9.7%) of 4588 pregnant women.[13] At age 1 year, 23.4% of infants born to seropositive mothers had died, as had 10.8% of infants born to seronegative mothers. The vertical transmission rate of HIV was estimated at approximately 25%. These data indicate that about 61.2% of HIV-infected infants died in infancy since the observed overall mortality rate of 234 per 1000 live births in the cohort of children born to infected mothers = [the proportion of children infected with HIV (25%) × their MR (unknown)] + [the proportion of children not infected with HIV (75%) × their MR (108 per 1000 live births)].

In Zaire, a country with a high MR for the group younger than 5 years,[12] 468 infants born to seropositive mothers in 1986-1987 were followed up for 1 year[9]; 100 (21.4%) of the infants died. The study revealed a mother-to-child transmission rate of 39% and suggested that mothers in more advanced stages of HIV disease might be more likely to transmit the infection to their infants. If the infant MR (100)[14] for Zaire in 1986 is assumed to apply to the proportion of newborns not infected with HIV, then approximately 40% of the HIV-infected children can be inferred to have died in infancy.

No comparable studies have been reported from countries classified by the United Nations Children's Fund as having medium MR for children under 5 years old in 1987.

Several studies have been reported from highly developed European countries with a low MR for this age group (Table 2).[7,8,15] In addition to the mother-to-child transmission rates shown in Table 2, two other studies in the United States have also shown rates of about 30%.[16,17]

Based on the foregoing, a mother-to-child transmission frequency of 40% was assumed to apply to countries with very high or high MRs for children younger than 5 years. This vertical transmission rate is higher than that reported for Haiti,[13] and approximately equal to that reported for Zaire.[9] However, a bias reported in the Haitian study may have resulted in an artificially low estimate of vertical transmission.[13] We estimated that 50% of HIV-infected infants might die in infancy in countries with very high MRs for those younger than 5 years, and 40% might die in countries with high rates. Infant death rates are generally higher in countries with very high MRs for those younger than 5 years than in countries with high rates (Table 1), and deaths from HIV infection in infancy might be expected to parallel baseline infant MRs.

Table 2.—Mother-to-Child Infection Studies in Highly Developed Countries*

Source, y	No. of HIV-Infected Children	No. (%) Dead in Infancy	Estimated Mother-to-Child HIV Transmission Rate, %
Blanche et al,[7] 1989	32	5 (15.6)	30
European Collaborative Study,[15] 1991	64	11 (17)	13
Italian Multicentre Study,[8] 1988	486	$\geq$14 ($\geq$8.5)	33

*HIV indicates human immunodeficiency virus.

Based on information for children younger than 5 years in countries with low MRs, a 30% mother-to-infant transmission rate was assumed for countries with medium and low MRs. For the 29 countries in the medium group, 25% of HIV-infected infants were assumed to die in infancy; for the 39 countries in the low group, 15% of HIV-infected infants were assumed to die in the first year of life.

Mortality in HIV-infected children who survive infancy has not been determined. However, because of the high frequency of symptomatic infections, mortality is likely to be substantial. The MR among HIV-infected children younger than 5 years is expected to increase as the overall MR for all children younger than 5 years in a country increases. We thus assumed that a total of 85%, 75%, 60%, and 50% of HIV-infected newborns would die before reaching age 5 years in the very high, high, medium, and low MR groups of children younger than 5 years, respectively. Among HIV-infected children who survive 1 year, these assumptions correspond with MRs of approximately 70%, 60%, 50%, and 40% in the very high, high, medium, and low MR categories, respectively, for children younger than 5 years.

The Mathematical Model

Maternal infection rates from 0% to 50% were applied to total births in 1987 for individual countries or groups of countries to obtain the number of births to mothers with and without HIV infection. We calculated the number of HIV-infected infants born

Table 3.—Application of the Mathematical Model for Countries With Very High Mortality (MR) Rates for Children Under 5 Years old (VHU5MR) at One Assumed Prevalence of Maternal Human Immunodeficieny Virus (HIV) Infection (1%)

Variable No.	Variable	No.	Calculation*
1	Births in 1987	24 695 000	. . .
2	Proportion of mothers infected with HIV	0.01	. . .
3	Births among HIV-infected mothers	246 950	No. 1 x No. 2
4	Newborns infected	98 780	No. 3 x 0.4 (the assumed vertical transmission rate in VHU5MR countries)
5	Births among uninfected women	24 448 050	No. 1 x (1.0 − No. 2)
6	Uninfected newborns	24 596 220	No. 5 + (No. 3 − No. 4)
	Deaths Among Uninfected Newborns		
7	Infant MR (129) in 1987	3 172 912	No. 6 x 129/1000 (the median infant mortality rate for VHU5MR in 1987)
8	1-5 year MR (80) in 1987	1 967 698	No. 6 x 80/1000 (the median 1- to 5-y MR for VHU5MR countries in 1987)
9	Total deaths before age 5 years for uninfected newborns	5 140 610	No. 7 + No. 8
10	Baseline death incidence from 1 to 5 y	0.092	No. 8 (baseline 1- to 5-y deaths in uninfected infants) ÷ [(No. 5 (uninfected infants) − No. 7 (baseline infant deaths in uninfected infants)]
	Deaths Among HIV-Infected Newborns		
11	Total 1st y among HIV infected	49 390	No. 4 (infected newborns) x 0.5 (the assumed total mortality for VHU5MR countries in first year of life)
12	1st y other causes	12 743	No. 4 (infected newborns) x 129/1000 live births (the 1987 median infant mortality for VHU5MR countries)
13	1st y HIV-caused	36 647	No. 11 (total infant deaths) − No. 12 (deaths from other causes in infants)
14	Total 1-5 y among HIV infected	34 573	No. 4 (infected newborns) x 0.35 (the assumed total mortality for VHU5MR countries from 1 to 5 y)
15	1-5 y causes other than HIV	4 536	[No. 4 (infected newborns) − No. 11 (infant deaths)] x No. 10 (baseline median 1 to 5 y mortality rate for VHU5MR countries)
16	1-5 y HIV-caused	30 037	No. 14 (total 1-5 year deaths) – No. 15 (deaths among 1- to 5-year-olds from other causes)
17	Total HIV-caused deaths before age 5 y in infected newborns	66 684	No. 13 (1st year HIV-caused) + No. 16 (1 to 5 y HIV-caused)
18	Total deaths from causes other than HIV before age 5 y in infected newborns	17 279	No. 12 (1st year other causes) + No. 15 (1 to 5 y other causes)
19	Total deaths before age 5 y in infected newborns	83 963	No. 17 + No. 18
20	Overall MR for children under 5 y	211.6	[(No. 9 + No. 19) ÷ No. 1] x 1000
	% of Children Dying Within 5 y		
21	HIV caused	0.3	(No. 17/No. 1) x 100
22	Non–HIV caused	20.9	[(No. 18 + No. 9) ÷ No. 1] x 100
23	% of deaths before age <5 y HIV caused	1.3	[No. 17 ÷ (No. 19 + No. 9)] x 100
24	Overall 1-5 y MR	81.1	[(No. 14 + No. 8) ÷ No. 1] x 1000

*Countries with very high MRs for children under 5 years were defined as those with 170 deaths per 1000 live births and higher. (Data for 1987 from UNICEF's *The State of the World's Children 1989.*[12]) The numbers refer to numbered lines on the left of the chart, which identify the value of the variable used in the equation.

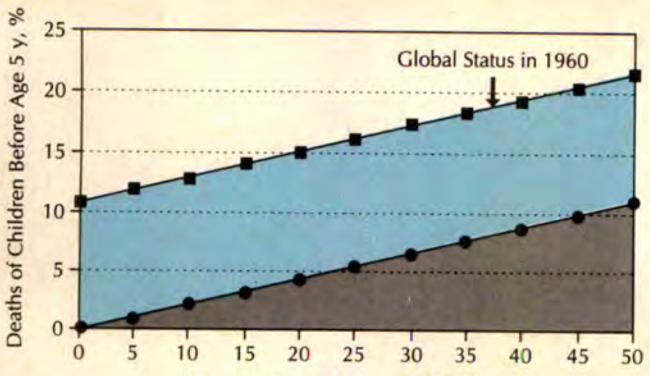

Fig 1.—*Global effect of various levels of maternal human immunodeficiency virus (HIV) infection on percentage of newborns dying within 5 years. Line with squares represents the total from all causes; line with plus signs, HIV-related causes.*

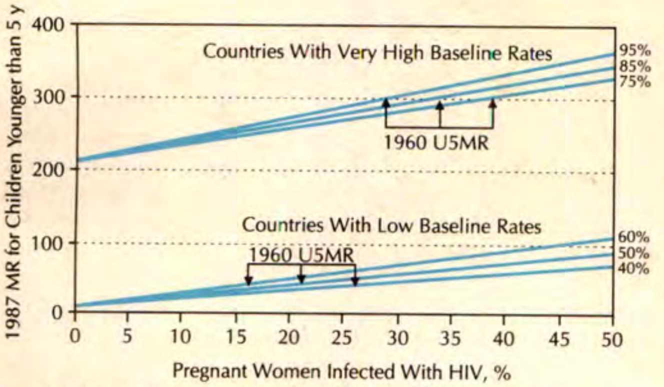

Fig 2.—*Mortality rates (MRs) for children younger than 5 years (U5MR) for 1987. Comparative impact of various levels of maternal human immunodeficiency virus (HIV) infection in countries with low vs very high baseline childhood MRs. (Overall mortality by age 5 years for HIV-infected children is also shown for +10% of the values assumed in Table 1.)*

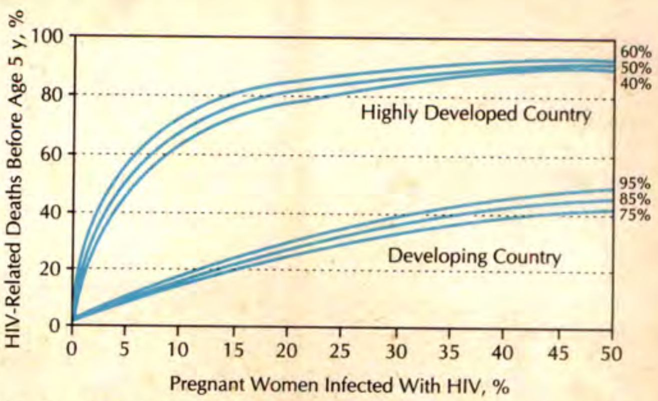

Fig 3.—*Percentage of human immunodeficiency virus (HIV)–caused deaths in children younger than 5 years. Impact of various levels of maternal HIV infection in two countries with widely differing baseline childhood mortalities. (Overall mortality by 5 years for HIV-infected children is also shown for ±10% of the values assumed for countries in their mortality rate grouping in Table 1.)*

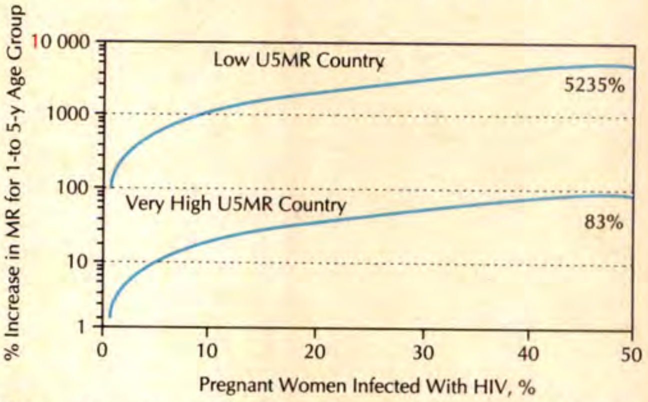

Fig 4.—*Comparison of percentage increase in mortality rates (MRs) for the 1- to 5-year age group between two countries with widely differing baseline childhood MRs. U5MR indicates MR for children under age 5 years; HIV, human immunodeficiency virus.*

to infected mothers in accordance with mother-to-child transmission rates for the MR group to which the country belonged in 1987 (Table 1). An example of the data and formulas used in a single application with an assumed maternal HIV infection prevalence of 1% is given in Table 3.

This example illustrates how the assumptions in Table 1, combined with baseline births, frequency of maternal HIV infection, infant MR, and MR for 1- to 5-year-olds in countries with very high rates of death among children younger than 5 years, can be used to establish changes in the overall MR for children younger than 5 years, the percentage of children dying within 5 years, the percentage of HIV-caused deaths in children younger than 5 years, and MRs for 1- to 5-year-olds.

RESULTS

On a global basis, HIV infection would account for about one third of all childhood deaths at a maternal HIV infection prevalence of 25% and would become the cause of most childhood deaths at a maternal prevalence of 45% (Fig 1). A global prevalence of 35% to 40% would be needed to offset the enormous global reductions in childhood mortality achieved from 1960 to 1987.

The impact of mortality from perinatal HIV infections will be far more evident among countries with low MRs for children younger than 5 years (Fig 2). For such countries, the MR for children younger than 5 years will double at a maternal HIV infection prevalence of about 9%, and will revert to average 1960 levels at maternal HIV infection levels of about 23%. In comparison, the MR for children younger than 5 years in countries with very high MRs for children younger than 5 years will not double until maternal infection prevalence exceeds 50%; about 35% of all pregnant women in these countries need to be infected with HIV to offset the enormous gains in child survival that have occurred since 1960. Countries in the high and medium MR groups for children younger than 5 years lie between these extremes.

Thus, if one compares the proportion of HIV-caused deaths of children in a highly developed European country (Sweden) with a developing sub-Saharan African country (Uganda), the impact of HIV will be relatively much greater in Sweden (Fig 3). The HIV infection would account for about one third of all deaths of children at a maternal HIV infection level of 2.4% in Sweden, and for more than half of all deaths of children at a prevalence of 4.8%. In contrast, HIV infection would account for one third of childhood deaths in Uganda at a maternal HIV infection level of 30%, and would not account for most childhood deaths until more than half of all pregnant women became infected with the virus.

Mortality rates for infants have exceeded those for 1- to 5-year-olds in all countries of the world since at least 1960. A reversal in this relationship, with the MR for the 1- to 5-year age group exceeding the MR for infants, is predicted for countries with low MRs for chil-

Table 4.—Distribution of Perinatal Human Immunodeficiency Virus (HIV) Infections and HIV-Caused Deaths in Children Under 5 Years Old by Geographic Region

	Annual Perinatal Infections		Annual Deaths Before Age 5 Years*	
Maternal Infection Prevalence, %	Sub-Saharan Africa	Europe and North America	Sub-Saharan Africa	Europe and North America
1	77 000	24 000	51 000	12 000
5	384 000	120 000	254 000	58 000

*The model actually estimates deaths in a cohort of births followed until age 5 years. Annual deaths will be identical if birth, infection, and mortality data remain stable over a 5-year period.

dren younger than 5 years, if the maternal HIV-infection prevalence reaches 10% to 15%.

The greatest predicted increase in death rates will be for the 1- to 5-year-olds in highly developed countries (Fig 4). In a country with a baseline MR for the 1- to 5-year age group of 3 per 1000 (a low MR for children younger than 5 years), the MR for 1- to 5-year-olds will increase by approximately 100% at a maternal HIV infection prevalence of about 3%. In comparison, a country with a very high MR for children younger than 5 years would see its MR for the 1- to 5-year age group increase by only about 5% at this prevalence.

Although the impact of perinatal HIV infections is likely to be particularly obvious in highly developed countries in North America and Western Europe, the numbers of perinatal HIV infections and deaths will be far greater in the sub-Saharan African countries, which account for about 20 million births annually (Table 4).

COMMENT

Diarrheal disease, respiratory infections, and vaccine-preventable deaths were the main causes of childhood mortality in 1987, with each responsible for about 30% of all childhood deaths worldwide.[12] While HIV infection is unlikely to surpass these diseases as the most common cause of death in children worldwide (ie, responsible for more than 30% of all childhood deaths), it is becoming an increasingly important cause of death in women and children in both developing and developed countries. Indeed, HIV infection has doubtlessly already emerged as the principal cause of death in some populations.

Chin et al[11] evaluated the effect of AIDS on MRs of children younger than 5 years at three different assumed levels of HIV infection of pregnant women in a single assumed population with a baseline MR of children younger than 5 years of 100 deaths per 1000 live births, a mother-to-infant HIV transmission rate of 25%, and an overall mortality rate of 80% in the first 5 years for HIV-infected newborns. The effect on outcome of altering the baseline MR for children younger than 5 years was not evaluated. At maternal HIV infection prevalence levels of 5%, 10%, and 20%, the death rates for children under 5 years old were predicted to increase by 9%, 18%, and 36%, respectively. We predicted comparable increases in the MRs for children younger than 5 years on a global basis (11%, 20% and 40%, respectively) for these maternal HIV infection prevalences.

Our model indicates that, in many areas, HIV infection has had a substantial effect on childhood rates of death. A population-based serosurvey in Rwanda found that 21% of urban women were infected with the HIV.[6] At this level, given Rwanda's overall baseline birth and mortality data for 1987, the child MR will have increased by 26%. The actual increase will probably be greater because MRs for children younger than 5 years tend to be lower in urban areas, and many additional deaths may result when these mothers' deaths produce large numbers of orphans.[18] Relatively high rates of maternal HIV infection have been reported from other African countries as well: 2% of pregnant women in Nairobi, Kenya[19]; 6% of pregnant women in Kinshasa, Zaire[9]; 14% of pregnant women in Uganda[20]; and 16% to 19% of pregnant women in Malawi.[21]

Seroprevalence rates of HIV infection among women in Europe and the United States have been much lower. A nationwide population-based survey in the United States, using blood collected from infants on filter paper for routine metabolic testing, found that 0.15% of women were infected in 1988, but rates ranged from 0% in some areas to more than 2% in some parts of New York City and South Florida.[1,22,23] Even at low national seroprevalence rates, AIDS was reported to rank as the ninth leading cause of death in 1987 for 1- to 5-year-old American children and to account for approximately 1.5% of all deaths in this age group.[24] Our model predicts that about 5% of all deaths in the United States in this age group will be caused by HIV infection at a maternal prevalence of 0.15%. The observed proportion of deaths due to the HIV infection may be lower than our predicted value because many HIV-attributable deaths may go unrecognized or be attributed to other causes.

Although we have applied the model only to countries, it can also be applied to subpopulations within countries when the childhood mortality and other variables of the population needed in the model can be estimated. In the United States, for instance, HIV infection disproportionately affects blacks and Hispanics,[25] groups already at higher risk of infant mortality.[26]

The greatest morbidity and mortality burden from perinatal HIV is expected in sub-Saharan Africa. Cases and number of deaths are larger, even at comparable rates of maternal HIV infection, because the number of births is greater and the mother-to-infant transmission frequency and MRs among children under 5 years old are higher. In addition, seroprevalence among pregnant women is also substantially higher in sub-Saharan Africa than in Europe and North America. Indeed, Preble[18] has estimated that HIV infection will cause as many as one half million deaths annually by the year 2000 in 10 Central and East African countries, should maternal HIV infection prevalence reach 30%. With the use of 1987 demographic data for these same countries and values in Table 1 appropriate for the MR for children younger than 5 years in each country, our model predicts about 650 000 HIV-caused deaths of children when the maternal HIV infection prevalence reaches this level. Even more deaths than this would be expected if increased numbers of births in the year 2000 were used in the model. Our estimated MRs for children younger than 5 years is higher than the maximum estimate of Preble[18] (235 and 189 per 1000 live births, respectively) for a maternal infection prevalence of 30% in these countries. These differences appear to derive largely from Preble's assuming a continuing decline in the MR for children younger than 5 years as projected before the advent of the AIDS epidemic. However, rates of non–HIV-related deaths of children may themselves increase consequent to the HIV epidemic, since the majority of children orphaned by HIV-caused deaths of their mothers will be uninfected but likely to experience sharply increased risks of death of uncertain magnitude. Also, access to and quality of care may decline for children not infected with the HIV in areas of high incidence of HIV infection as these areas become overburdened by HIV-caused illnesses. These factors may serve to offset any overall trend of improved child survival in children both with and without HIV infection.

With the use of 1987 data for Haiti and values appropriate for a country with a very high MR for children younger than 5 years, our model predicts an increase in the country's infant MR from 111 to 126, an 11.9% increase, at the observed maternal HIV infection prevalence of 9.7%. This is very close to the actual reported increase of 11.7% in the overall infant MR in this country.[13]

We believe our model can usefully evaluate the likely effect of HIV infection on infant and child survival in any population for which demographic information and a maternal HIV infection prevalence representative of that population are available. The model may also be helpful in estimating the value of single variables, including seroprevalence, when the values of all other variables can be specified.

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Clinical and Endocrinologic Manifestations in Perinatally Human Immunodeficiency Virus Type 1–Infected Children Aged 5 Years or Older

Philippe Lepage, MD; Philippe Van de Perre, MD; Guy Van Vliet, MD, PhD; François Nsengumuremyi, MD; Christiaan Van Goethem, MD; Philippe Kestelyn, MD; Philippe Msellati, MD; Deo-Gratias Hitimana, MD

• Sixteen human immunodeficiency virus type 1 (HIV-1)–seropositive children aged 5 to 12 years (nine girls and seven boys), born to HIV-1–infected mothers, were diagnosed between 1984 and 1987 in Kigali, Rwanda. They were compared with a group of age- and sex-matched HIV-1–seronegative children consecutively selected from the outpatient department. Two subjects were asymptomatic. Chronic cough was the most frequent symptom (seven of 16 patients). The most common signs were short stature (12 of 16 patients), low weight for age (seven of 16 patients), chronic parotitis (eight of 16 patients), persistent generalized lymphadenopathy (seven of 16 patients), and pulmonary tuberculosis (four of 16 patients). Lymphoid interstitial pneumonitis was diagnosed on radiologic grounds in five of 16 patients. Evidence of perivasculitis in the fundus was noted in three of 16 patients. Two children died during the study period (mean duration of follow-up, 40 months; range, 27 to 62 months); none of the other children had life-threatening infection or loss of developmental milestones. Immunologic assessment in the 16 children revealed high levels of IgG, decreased CD4⁺/CD8⁺ ratio, and skin test anergy. Endocrinologic investigations revealed normal thyroid function and normal basal human growth hormone levels but low basal insulinlike growth factor I levels (0.21±0.07 vs 0.44±0.20 U/mL for controls). In Kigali, perinatally HIV-1–infected children surviving beyond 5 years of age often present with moderate signs and symptoms, principally pulmonary involvement, chronic parotitis, and persistent generalized lymphadenopathy. Short stature is the major clinical manifestation in these patients and may be due, in part, to low growth hormone secretion rather than to malnutrition.

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Most previous clinical and epidemiologic studies involving human immunodeficiency virus type 1 (HIV-1) in children have focused on infants and young children.[1-6] These patients were characterized by the severity of pediatric HIV-1 infection, including opportunistic infections, severe bacterial infections,[7,8] and neurologic involvement.[9,10] The broad spectrum of HIV-1 infection recognized in adult patients has also recently been described among pediatric patients, including patients with minor complaints or even "healthy carriers."[11-13] Based on mathematical modeling, Auger et al[14] have determined that the median incubation period for perinatally acquired acquired immunodeficiency syndrome (AIDS) was 4.8 years. Twenty percent of the infected newborns developed AIDS in the first year of life, with the remainder developing AIDS at a rate of 8% per year.[14] Thus, not all children infected perinatally with HIV-1 progress rapidly to AIDS. However, data regarding HIV-1 infected children are limited beyond infancy,[15-19] and follow-up information with relatively large series of children older than 5 years is lacking.

Herein, we describe our clinical experience with children perinatally infected with HIV-1 who survived longer than 5 years in Kigali, Rwanda.

PATIENTS AND METHODS

Selection of Patients

From 1984 to 1987, only 16 (3%) of 537 symptomatic HIV-1–infected children born to HIV-1–seropositive mothers who were diagnosed at the Pediatric Department of the Centre Hospitalier de Kigali were aged 5 years or older. These 16 children (patients) were enrolled prospectively after verbal consent was obtained from their mother or guardian. At the time of enrollment, their ages varied from 5 to 12 years (mean, 6.5 years); there were nine boys and seven girls. The mean follow-up at the time of this writing was 40 months (range, 27 to 62 months), during which time the children were clinically and biologically evaluated at least every 6 months. The patients were matched for age, sex, and ethnic origin with 16 HIV-1–seronegative subjects (controls). These

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From the Departments of Pediatrics (Drs Lepage, Nsengumuremyi, Van Goethem, and Hitimana) and Ophthalmology (Dr Kestelyn), Centre Hospitalier de Kigali (Rwanda); the National Reference Laboratory, AIDS Control Program, Kigali (Dr Van de Perre); the Department of Pediatrics, Université Libre de Bruxelles (Belgium) (Dr Van Vliet); and INSERM, Unité 330, Bordeaux, France (Dr Msellati). Dr Van Vliet is now with the Research Center and Endocrine Service, Department of Pediatrics, Hôpital St Justine, Université de Montréal, Québec.

Reprint requests to 12, Eve Taille Cuvelier, 7000 Nous, Belgium (Dr Lepage).

control subjects were consecutively selected at the outpatient department, where they were seen for minor complaints.

Clinical Assessment

Clinical evaluation included regular chest roentgenography and eye fundus examinations. Short stature was defined as a height less than the fifth percentile for age and sex on the National Centre for Health Statistics' curves. Height SD scores and ratio of weight to the 50th percentile for chronologic age were calculated with use of the tables of Tanner et al[20] for British children.

Serologic Methods

All serum samples from the children, as well as the samples obtained from the mothers of the patients, were screened by a commercial immuonenzymatic assay (Vironostika, Organon Teknika, Boxtel, the Netherlands). Serum samples that were positive by immunoenzymatic assay were further confirmed by a commercial Western blot technique (Du Pont de Nemours, Wilmington, Del), in which a positive test was defined by the presence of at least one reactive band to a HIV-1 core protein (p17, p24, p55) plus at least one reactive band to an HIV-1 envelope protein (gp41, gp120, gp160).[21]

Immunologic Methods

Delayed-hypersensitivity skin testing was performed by means of seven recall antigens (Multitest, Bio Merieux, Narcy-L'Etoile, France), and the diameter of the induration was measured 3 days after exposure. Mononuclear cell subpopulations were quantified with an indirect immunofluorescent technique and monoclonal antibodies: OKT4 for helper-inducer T cells and OKT8 for suppressor-cytotoxic T cells (Ortho Diagnostic System, Raritan, NJ). Serum IgG, IgA, and IgM levels were measured by radial immunodiffusion (Nor Partigen, Behring, Narburg, Federal Republic of Germany).

Endocrinologic Methods

Levels of serum thyroid hormones and thyrotropin were measured with commercially available kits (Amersham, London, England), as was human growth hormone (GH) (Pharmacia, Uppsala, Sweden). The insulinlike growth factor I (IGF-I) level was measured by radioimmunoassay after acid-ethanol extraction (to decrease the interference of the binding proteins) with iodine 125–labeled IGF-I (Nichols, San Juan Capistrano, Calif) and a polyclonal antibody against synthetic IGF-I.[22]

Statistical Methods

Comparisons between the groups of children were performed with the Wilcoxon Rank-Sum test.

RESULTS

All of the patients were born to HIV-1–infected mothers. Six of the 16 mothers had died, five of them had died of AIDS as diagnosed by the World Health Organization's provisional clinical case definition of AIDS in adults. None of the 16 patients had a history of blood transfusion before the onset of signs or symptoms related to HIV-1 infection. Parenteral treatments had been performed at the Centre Hospitalier de Kigali and in the health centers surrounding the hospital, where sterilization of medical materials is routinely performed.

Clinical and Anthropometric Features

Two patients were asymptomatic. Chronic cough was the most frequently observed symptom (Table 1). The most common signs were short stature, chronic parotitis, persistent generalized lymphadenopathy, hepatosplenomegaly, and pulmonary tuberculosis (Table 1). Chronic otitis media, clubbing of the digits, herpes zoster infection, and chronic urticaria were also noted. Lymphoid interstitial pneumonitis was diagnosed on radiologic grounds (chronic diffuse bilateral micromodular infiltrate) in 31% of the patients. Evidence of perivasculitis on the fundus was noted in 19% of the patients. No patient had persistent oral thrush.

Table 1.—Clinical Manifestations in African Children Perinatally Infected by Human Immunodeficiency Virus Type 1 and Aged 5 Years or Older

Clinical Manifestation	No. (%) of Patients
Short stature*	12 (75)
Chronic cough	7 (44)
Chronic parotitis	8 (50)
Persistent generalized lymphadenopathy	7 (44)
Lymphoid interstitial pneumonitis	5 (31)
Hepatomegaly or hepatosplenomegaly	5 (31)
Pulmonary tuberculosis	4 (25)
Perivasculitis (in the fundus)	3 (19)
Chronic otitis media	2 (13)
Herpes zoster infection	2 (13)

*Height less than fifth percentile for age and sex (National Centre for Health Statistics curves).

The 16 patients had markedly shorter stature than controls (SD score, −2.5±1.4 vs −0.4±0.8; $P<.0001$), but the weight, expressed in percent of median weight for height age, was similar in both groups (96%±8% vs 94%±8%; $P>.5$). Height velocity, calculated in the 12 months preceding the more recent clinical evaluation, was 4.1±1.8 cm/y (SD of height velocity for age=−1.88±2.18 [SD] for age).

Two children died during the study period: one of AIDS and one of liver cirrhosis. None of the other children had life-threatening infection or loss of developmental milestones.

Immunologic Evaluation

Compared with controls, the 16 patients had an increased concentration of serum protein (10.2±0.9 vs 7.4±0.7 g/L; $P<.001$) and a decreased concentration of serum prealbumin (0.13±0.04 vs 0.18±0.03 g/L; $P<.01$). The serum concentration of IgG in the patients was statistically increased compared with controls (40.8±15.4 vs 16.9±11.9 g/L; $P<.01$).

Profound cell-mediated immune impairment was observed in the patients, with a dramatic decrease in the percentage of $CD4^+$ cells (13%±7% vs 39%±5% in controls; $P<.01$) and in the $CD4^+/CD8^+$ ratio (0.33±0.26 vs 1.82±0.35 in controls; $P<.01$). These patients also had a severe defect of delayed hypersensitivity, as measured by skin testing, with much smaller indurations (mean total induration, 4.5±3.1 mm vs 15.4±6.9 mm in controls; $P<.01$).

Endocrinologic Evaluation

Endocrinologic investigations were performed in 11 patients and in 11 matched controls. Mean levels of serum thyroid hormones and thyrotropin were similar among patients and seronegative controls (Table 2). Mean IGF-I concentrations were lower in patients compared with controls, while mean basal GH levels were similar (Table 2).

Table 2.—Endocrinologic Findings in African Children Perinatally Infected by Human Immunodeficiency Virus Type 1 and Aged 5 Years or Older*

	Patients (n=11)	Controls (n=11)	*P*
Thyrotropin, μU/mL	2.6 (1.3)	2.3 (0.9)	NS
T_3, mmol/L	2.99 (0.85)	2.36 (0.82)	NS
T_4, mmol/L	108 (32)	109 (27)	NS
IGF-I, U/L	219 (70)	440 (200)	.004
GH, μg/L	1.9 (1.5)	3.2 (3.6)	NS

*Values are means (SDs). T_3 indicates triiodothyronine; T_4, thyroxine; IGF-I, insulinlike growth factor-I; GH, basal plasma growth hormone; and NS, not significant.

COMMENT

These 16 patients with a prolonged, paucisymptomatic course of HIV-1 infection represented only 3% of the symptomatic HIV-1–infected children seen in our hospital from 1984 to 1987. None of the 14 survivors had life-threatening infection, neoplasia, or neurologic impairment during the study period (mean follow-up, 40 months). None had any other known risk factor for HIV-1 acquisition than having an HIV-1–seropositive mother (some of whom died of AIDS), strongly suggesting a maternally acquired infection.

Most of these children presented with signs such as chronic parotitis, generalized lymphadenopathy, and lymphoid interstitial pneumonitis. Previous studies[12,16,19] have shown that generalized lymphadenopathy and lymphoid interstitial pneumonitis are associated with a favorable outcome in HIV-1–infected children. These clinical features resemble the "diffuse infiltrative lymphocytosis syndrome" recently described in HIV-infected adults from New York by Itescu et al.[23] In these patients with the diffuse infiltrative lymphocytosis syndrome, the prevalence of HLA-DR5 subtype JVM—a phenotype more frequently encountered in black subjects than in white subjects—and the number of circulating $CD8^+$ cells was unusually high.[23] However, in our series, the number of circulating $CD8^+$ cells was not higher in the patients compared with pediatric patients with AIDS diagnosed at the Centre Hospitalier de Kigali (Rwanda) (data not shown).

Despite their clinical stability, these children had major immunologic dysfunctions of both their humoral and cell-mediated immune systems. The high level of circulating immunoglobulins, particularly of the IgG class, suggests an intense polyclonal B-cell activation in our patients. Usually, this B-cell abnormality is associated with a poor antibody response to new antigens.[24,25] We have recently shown[26] that 14 of the 16 patients had specific anti–HIV-1 IgM, which persisted during the entire study period, and that 11 of them had IgM antibodies directed to HIV-1 envelope proteins. It is not yet clear whether these specific IgM antibodies have protective characteristics. Severe cell-mediated impairment was manifested by low numbers of $CD4^+$ cells, decreased $CD4^+/CD8^+$ ratios, and skin test anergy.

The most striking clinical characteristic of these patients was short stature. Growth failure has recently been described in children with perinatal and postnatal HIV-1 infection,[27] but its mechanisms remain unknown. While malnutrition, chronic illness, and stress probably play a role, it is conceivable that endocrine factors contribute to the decreased growth. Indeed, Jospe and Powell[28] have recently described GH deficiency in an 8-year-old girl with perinatal HIV-1 infection. On the other hand, Laue et al[27] found low GH responses to two provocative stimuli in only one of nine children with AIDS and low IGF-I levels but normal GH levels in another child, suggesting that the endocrine features of this syndrome are heterogeneous. Five of nine patients in their study were receiving nutritional support (by either the enteral or parenteral route), and it is known that nutritional rehabilitation restores the low IGF-I levels of malnourished patients to normal.[29] Furthermore, the assay for IGF-I used by Laue et al does not involve prior extraction of plasma to remove IGF binding proteins, and this may lead to spuriously high IGF-I levels.[30] The HIV-1–infected patients described herein had a mean plasma IGF-I level after acid-ethanol extraction of less than 50% of that observed in a group of matched controls living in the same environment. This could be due to either nutritional factors or to a lower GH secretion in the HIV-1–infected children. Except for one child with liver cirrhosis, none of the 15 remaining patients had evidence of liver function abnormalities that could explain low levels of IGF-I. The fact that basal plasma GH levels were not elevated in the HIV-1–infected children together with the similar weight-for-height in both groups suggest that overt malnutrition is not the explanation for the lower IGF-I levels. Unfortunately, due to limited technical facilities in Rwanda, we were not able to perform pituitary stimulation tests, such as measurement of thyrotropin over time after stimulation with thyrotropin-releasing hormone or GH secretion after glucagon secretion. A definitive conclusion about the GH secretory status of these HIV-1–infected children would require formal testing of the pituitary GH reserve.

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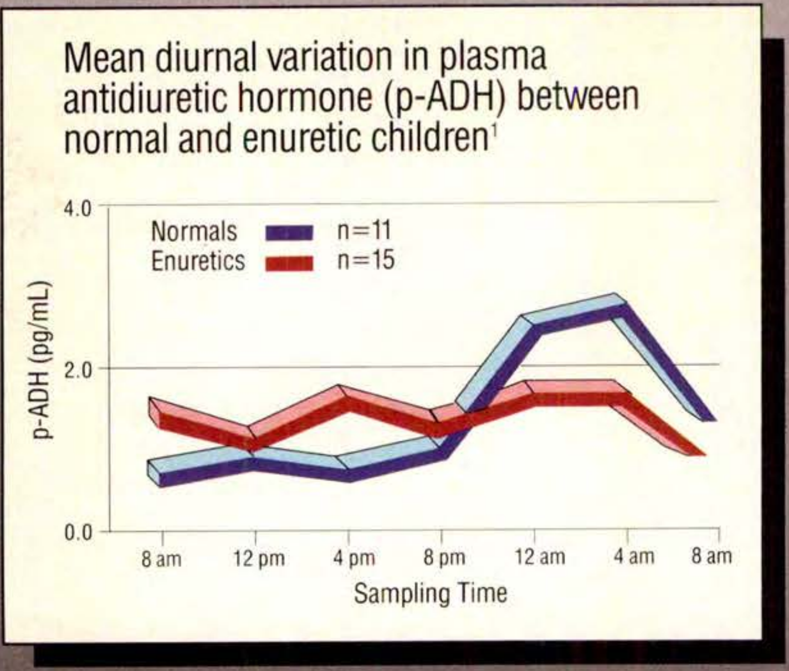
Trauma During Pregnancy: A Review of 79 Cases

Thomas J. Esposito, MD, MPH; David R. Gens, MD;
Lynn Gerber Smith, RN, MS; Ronald Scorpio, MD;
Timothy Buchman, MD
(*Arch Surg.* 1991;126:1073-1078)

Trauma in Pregnancy: Predicting Pregnancy Outcome

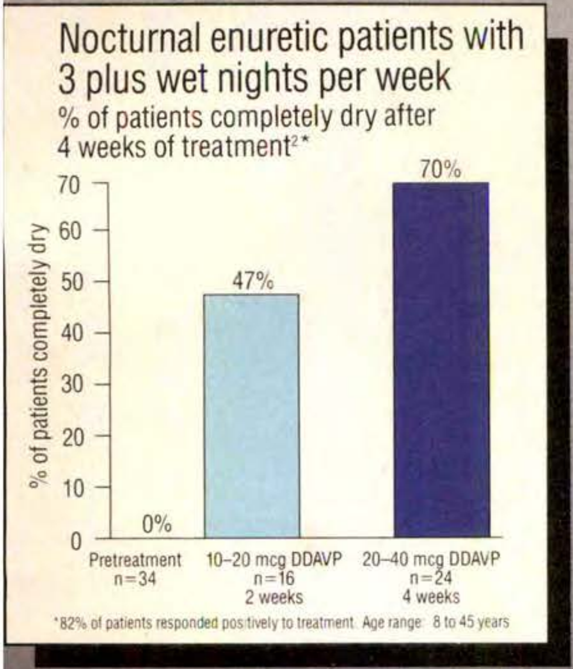
David P. Kissinger, MD; Grace S. Rozycki, MD;
John A Morris, Jr, MD; M. Margaret Knudson, MD;
Wayne S. Copes, PhD; Sue M. Bass, ScM;
H. Kendle Yates; Howard R. Champion, FRCS(Edin)
(*Arch Surg.* 1991;126:1079-1086)

Landmark study concludes: Enuretic children may lack diurnal rhythm of ADH common in non-enuretic children[1]


Mean diurnal variation in plasma antidiuretic hormone (p-ADH) between normal and enuretic children[1]

The ADH Deficit

The first physiologic treatment for nocturnal enuresis


Nocturnal enuretic patients with 3 plus wet nights per week
% of patients completely dry after 4 weeks of treatment[2]*

*82% of patients responded positively to treatment. Age range: 8 to 45 years

- DDAVP Nasal Spray, a synthetic analog of naturally occurring ADH, provides physiologic control of nighttime urine production in children 6 years of age or older[1-4]
- Clinically proven in all degrees of primary nocturnal enuresis, even in many patients resistant to imipramine and alarms[3]
- Easy to use — metered-dose nasal spray administered at bedtime
- Outstanding safety record in pediatric and adult patients[5]

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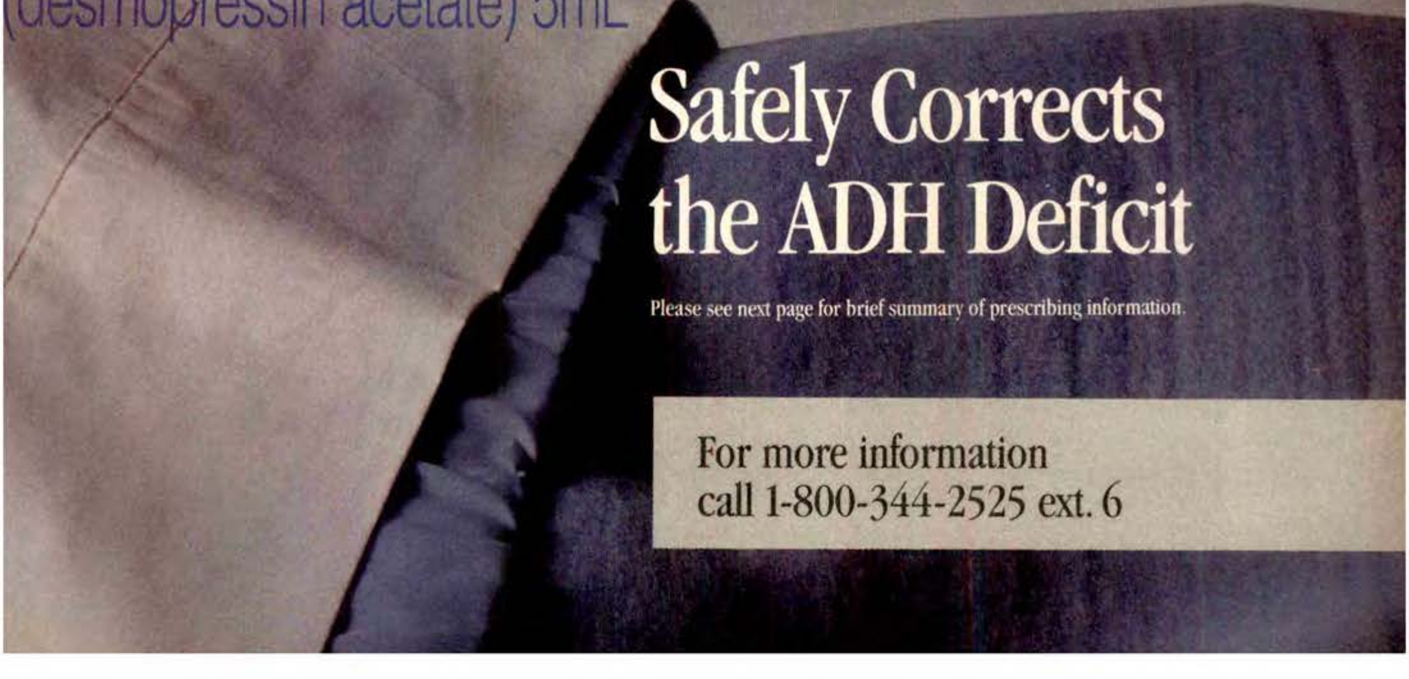

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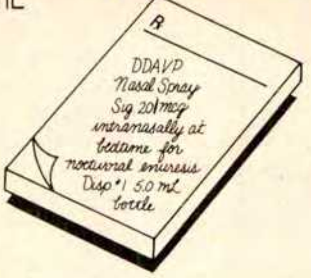

CONTRAINDICATION: Known hypersensitivity to DDAVP

WARNINGS: 1. For intranasal use only. 2. In very young and elderly patients in particular, fluid intake should be adjusted in order to decrease the potential occurrence of water intoxication and hyponatremia.

PRECAUTIONS:
General: DDAVP at high dosage has infrequently produced a slight elevation of blood pressure, which disappeared with a reduction in dosage. The drug should be used with caution in patients with coronary artery insufficiency and/or hypertensive cardiovascular disease because of possible rise in blood pressure.

Primary Nocturnal Enuresis: If changes in the nasal mucosa have occurred, unreliable absorption may result. DDAVP intranasal solution should be discontinued until the nasal problems resolve.

Information for Patients: Patients should be informed that the bottle accurately delivers 50 doses of 10 mcg each. Any solution remaining after 50 doses should be discarded since the amount delivered thereafter may be substantially less than 10 mcg of drug. No attempt should be made to transfer remaining solution to another bottle. Patients should be instructed to read accompanying directions on use of the spray pump carefully before use.

Laboratory Tests: For the healthy patient with primary nocturnal enuresis, serum electrolytes should be checked at least once if therapy is continued beyond 7 days.

DRUG INTERACTIONS: Although the pressor activity of DDAVP is very low compared to the antidiuretic activity, use of large doses of DDAVP with other pressor agents should only be done with careful patient monitoring.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY: Teratology studies in rats have shown no abnormalities. No further information is available.

PREGNANCY – CATEGORY B: Reproduction studies performed in rats and rabbits with doses up to 12.5 times the human intranasal dose (i.e. about 125 times the total adult human dose given systemically) have revealed no evidence of harm to the fetus due to desmopressin acetate. There are several publications of management of diabetes insipidus in pregnant women with no harm to the fetus reported; however, no controlled studies in pregnant women have been carried out. Published reports stress that, as opposed to preparations containing the natural hormones, DDAVP (desmopressin acetate) in antidiuretic doses has no uterotonic action, but the physician will have to weigh possible therapeutic advantages against possible dangers in each individual case.

NURSING MOTHERS: There have been no controlled studies in nursing mothers. A single study in a postpartum woman demonstrated a marked change in plasma, but little if any change in assayable DDAVP in breast milk following an intranasal dose of 10 mcg.

PEDIATRIC USE: Primary Nocturnal Enuresis: DDAVP has been used in childhood nocturnal enuresis. Short-term (4-8 weeks) DDAVP administration has been shown to be safe and modestly effective in children aged 6 years or older with severe childhood nocturnal enuresis. Adequately controlled studies with intranasal DDAVP in primary nocturnal enuresis have not been conducted beyond 4-8 weeks. The dose should be individually adjusted to achieve the best results.

There are reports of an occasional change in response with time, usually greater than 6 months. Some patients may show a decreased responsiveness, others a shortened duration of effect. There is no evidence this effect is due to the development of binding antibodies but may be due to a local inactivation of the peptide.

ADVERSE REACTIONS: Infrequently, high dosages have produced transient headache and nausea. Nasal congestion, rhinitis and flushing have also been reported occasionally along with mild abdominal cramps. These symptoms disappeared with reduction in dosage. Nosebleed, sore throat, cough and upper respiratory infections have also been reported.

The following table lists the percent of patients having adverse experiences without regard to relationship to study drug from the pooled pivotal study data for nocturnal enuresis.

ADVERSE REACTION	PLACEBO (N=59)	DDAVP 20 mcg (N=60)	DDAVP 40 mcg (N=61)
	%	%	%
BODY AS A WHOLE			
Abdominal Pain	0	2	2
Asthenia	0	0	2
Chills	0	0	2
Headache	0	2	5
Throat Pain	2	0	0
NERVOUS SYSTEM			
Depression	2	0	0
Dizziness	0	0	3
RESPIRATORY SYSTEM			
Epistaxis	2	3	0
Nostril Pain	0	2	0
Respiratory Infection	2	0	0
Rhinitis	2	8	3
CARDIOVASCULAR SYSTEM			
Vasodilation	2	0	0
DIGESTIVE SYSTEM			
Gastrointestinal Disorder	0	2	0
Nausea	0	0	2
SKIN & APPENDAGES			
Leg Rash	2	0	0
Rash	2	0	0
SPECIAL SENSES			
Conjunctivitis	0	2	0
Edema Eyes	0	2	0
Lachrymation Disorder	0	0	2

OVERDOSAGE: See adverse reactions above. In case of overdosage, the dose should be reduced, frequency of administration decreased, or the drug withdrawn according to the severity of the condition. There is no known specific antidote for DDAVP.

An oral LD_{50} has not been established. An intravenous dose of 2 mg/kg in mice demonstrated no effect.

HOW SUPPLIED: A 5 mL bottle with spray pump delivering 50 doses of 10 mcg (NDC 0075-2450-02). Keep refrigerated at 36°-46°F (2°-8°C). When traveling, product will maintain stability for up to 3 weeks when stored at room temperature, 72°F (22°C).

See product circular for full prescribing information. Rev. 6/89

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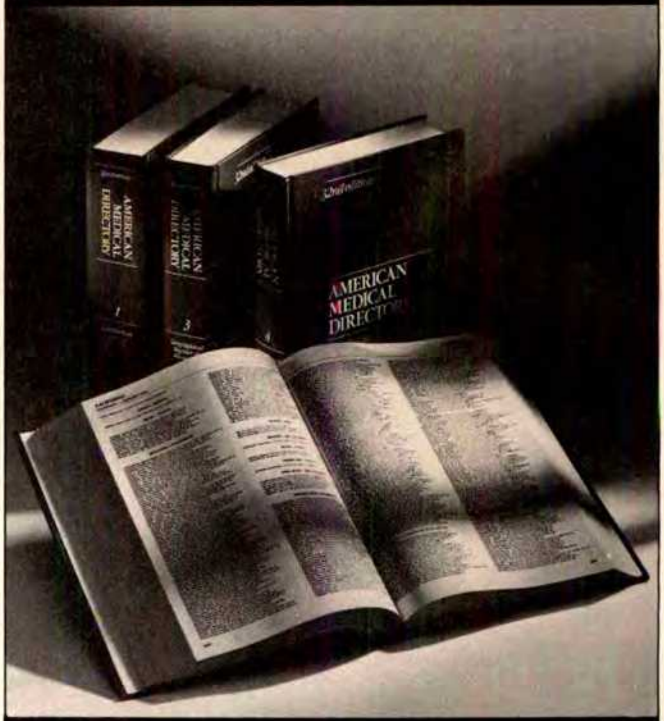

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Comparison of a Computer Tutorial With Other Methods for Teaching Well-Newborn Care

Larry W. Desch, MD; Maria T. Esquivel, MD; Sharon K. Anderson, MA

• Research using a computer-assisted instructional program developed for teaching well-newborn care is described. Third-year medical students were randomly assigned during their week-long nursery rotation into three groups to study the acceptability and effectiveness of using the computer-assisted instructional lessons. Group A, the control group, was not required to complete any additional educational task. Group B was assigned specific reading material. Group C completed the microcomputer-based tutorial. (The term *tutorial* is often used interchangeably to describe the computer-assisted instructional program.) Both groups B and C improved dramatically on a posttest in comparison with group A. There was no statistically significant difference between groups B and C on the improvement from pretest to posttest scores. However, significantly less time was spent by group C completing the tutorial compared with the total time spent reading by group B. The results of this study provide further illustration of the feasibility and effectiveness of using a computer-assisted instructional program for medical student education.

(*AJDC*. 1991;145:1255-1258)

During the past 15 years, there has been nearly an exponential growth rate in the development of computer-assisted instruction (CAI) for medical education. Computer-assisted instruction has moved from mainframe computers to personal microcomputers, which often make use of additional devices such as laser videodisk players to enhance the quality of the instruction.[1,2] The field of CAI for medical education has improved so dramatically that many of the early CAI programs, although they are less than 10 years old, appear now to be very simplistic and, perhaps, naive compared with current medical CAI.[3]

The ease with which CAI can be produced has also improved markedly over the past several years. The cost of development has also decreased. For example, it is now possible to develop locally the laser videodisks for use with CAI programs. In addition, many types of "authoring systems" are available that can expedite the production of CAI programs. These authoring systems are computer programs that function as a "shell" program to speed up the process of developing CAI.[4,5]

This article summarizes the development and initial evaluation of a CAI program developed for teaching various basic aspects of well-newborn care. The CAI program was developed primarily for medical student education, but has also been intermittently used by pediatric residents. However, the data presented are concerned only with the use by medical students.

SUBJECTS AND METHODS

A commercially available authoring system was used to develop the neonatal tutorial. This system, called UNISON, was selected partially because of its relatively low cost and ease of use, but primarily because it, unlike most other authoring systems, does not require the payment of royalties for the distribution of programs developed with UNISON.[6] A microcomputer with two floppy disk drives was used to both develop and present the CAI program.

The CAI program that was produced consisted of several short lessons presenting basic material, such as steps in the physical examination of the newborn, as well as some presentations on therapeutic measures, such as treatment of hyperbilirubinemia. Questions about material previously presented by the program were also posed intermittently. The tutorial is primarily linear, but some branching can be done that includes optional review of previously presented material. Accompanying the tutorial is a small booklet containing pictures and graphic illustrations, which are used to demonstrate visually a number of findings such as mongolian spots.

Three groups of third-year medical students at the Univer-

Department Editors.—*Hugh D. Allen, MD, Columbus, Ohio; Fredric Burg, MD, Philadelphia, Pa; Harold Levine, MPA, Galveston, Tex; Barbara Starfield, MD, Baltimore, Md; Larrie W. Greenberg, MD, Washington, DC*

Purpose.—*This department is intended to share information concerning educational efforts in the broad field of pediatrics. We welcome studies on the following topics: undergraduate and graduate education in medicine and allied health occupations; continuing education of health professionals; education of patients and families; and health education for the general public, the community, and organizations that contribute to the promotion and improvement of the health of children.*

Accepted for publication March 25, 1991.

From the Department of Child Health (Pediatrics) (Drs Desch and Esquivel); and the Division of Biostatistics, Department of Information Sciences, University of Missouri–Columbia School of Medicine (Ms Anderson).

Reprint requests to Department of Pediatrics, University of Wisconsin Medical School, 600 Highland Ave, Madison, WI 53792 (Dr Desch).

sity of Missouri–Columbia Medical School were selected during 1989 and 1990 to study the acceptability, effectiveness, and validity of using this neonatal CAI program. There were 26 students in each of these three groups. The well-nursery rotation for each group of the students lasted 1 week. All three groups were later subdivided into two subsets depending on whether they had taken their pediatrics rotation during the first half or the second half of their third year. This was done to determine whether there were any effects on the results obtained because the students had been exposed to clinical medical education for a longer period.

Participation by all of the subjects was purely voluntary and effort was made to ensure that the students did not believe that there would be positive or negative effects if they did or did not participate, respectively. Approval from the University of Missouri–Columbia School of Medicine's Institutional Review Board was obtained prior to the commencement of the project.

The third-year medical students who participated were selected into one of the three groups in a sequential random order. Attending physicians for these groups differed during the study periods; therefore, what was taught to them informally varied as well. Group A served as the true control group. These students were not given any additional educational intervention.

The second group, group B, was given specific instructions about the assigned reading that was required. A small paperback[7] was used for this reading material. Selected pages and, occasionally, particular paragraphs were listed as required reading. This textbook was not available to the students in the other groups. The students in group B were asked to keep track of their time spent reading. This group of students served as the attention-placebo group.

The students in group C served as the main experimental group. This group of students was given basic written instructions on how to use the microcomputer and was given the program on floppy disks and the accompanying book with pictures and diagrams. This group was also asked to keep track of their time spent working on the program. They were additionally requested to fill out an 11-item Likert scale questionnaire that asked questions about their interactions with the microcomputer and the CAI neonatal program. This scale will be described as an "acceptability index" in following discussions. The actual scale that was used has been published previously.[4]

Answers to questions on this scale helped to determine if the students believed, for example, that they "improved (their) knowledge about well-newborn care" and if the content of the tutorial was appropriate and understandable. Answers to other questions on the scale determined whether there were any problems with the use of the program and if the students appreciated the design features of the program, such as the brief quizzes presented and the ability to review.

In all three groups, a pretest and posttest were given to each student to complete. Both tests consisted of 20 multiple-choice questions (four choices each). Questions on the posttest were exactly the same as on the pretest, but were arranged in different order. The pretests for all groups were given shortly before the start of their nursery rotation or on the morning of the first day of the nursery rotation. The posttest was completed by the students on the last day of the rotation or the following day.

The questions that were used on the two tests were written, for the most part, so that the students could reflect on their experience rather than just recall facts. No questions were chosen that asked about material that was not specifically presented. Questions about topics that were of the most importance and were also likely topics to have been presented to the control group of students, for example, the etiology of hyperbilirubinemia, appeared on the survey. A convenience sample of five beginning third-year students was used to pilot test these questions. The mean score for this sample was 9.8.

The SAS statistical analysis computer program was used to organize and analyze the data using Kruskal-Wallis and Wilcoxon's rank sum nonparametric methods.[8]

Table 1.—Summary of Results in the Three Groups of Students*

	Group A (Control)	Group B (Book)	Group C (Computer)	*P*†
Pretest				
Mean (SD)	14.5 (2.00)	15.2 (2.61)	15.6 (2.16)	NS
Range	10-17	10-19	12-19	
Posttest				
Mean (SD)	16.7 (2.18)	18.8 (1.04)	19.4 (0.70)	.0001‡,§
Range	12-20	16-20	18-20	
Difference				
Mean (SD)	2.3 (1.31)	3.6 (2.22)	3.8 (2.09)	.0123‡,§
Range	0-5	(−1)-7	0-8	
Total time				
Mean (SD)	. . .	70.4 (8.2)	54.4 (7.9)	.0001
Range	. . .	60-85	45-70	
No.	. . .	14	17	

*The number of each was 26, except as indicated.

†Results from Kruskal-Wallis analysis. NS indicates not significant.

‡Post hoc analysis (using Wilcoxon's rank sum test): group B was significantly different from group A.

§Post hoc analysis: group C was significantly different from group A.

RESULTS

The results for the three groups are summarized in Table 1. Several students in groups B and C did not indicate the total time spent. However, the number missing is similar between the groups.

As was anticipated, groups B and C improved dramatically on their posttest in comparison with group A, in which no additional educational interventions were used. The results from Kruskal-Wallis nonparametric analysis demonstrated statistically significant ($P = .012$) differences in the change from pretest to posttest. Post hoc analysis revealed significant differences between group B and group A, as well as between group C and group A. Somewhat surprisingly, however, there was no statistically significant difference in the improvement from pretest to posttest scores between the group that was given assigned readings (group B) and the group using the computerized neonatal tutorial (group C). Group C demonstrated slightly better posttest scores as well as better improvement from pretest scores (19 vs 18 and 3.8 vs 3.6, respectively).

However, these two groups showed statistically significant differences in the time spent completing either the readings or the computerized tutorial ($P = .0001$). Group B spent a mean of 70 minutes, while group C spent about 20 minutes less time.

The data additionally demonstrate that there was a ceiling effect present that was not anticipated. Many students, especially those who took the pretest in the second half of their third year (first clinical year), achieved a relatively high score and, therefore, did not improve much on the posttest. Despite the ceiling effect, the different scores between the groups remain significant ($P = .0123$). The high pretest ceiling was not expected since the mean score from pilot testing of the test questions was 9.8.

Considering the subsets based on whether a student

Table 2.—Acceptability Index Results*

Question	First Half-Year Group (n=12), Mean (Range)	Second Half-Year Group (n=14), Mean (Range)
1	2.42 (2-3)	2.64 (2-3)
2	2.33 (2-3)	2.50 (2-3)
3	2.50 (2-3)	2.57 (2-3)
4	2.58 (2-3)	2.42 (2-3)
5	2.67 (2-3)	2.50 (2-3)
6	2.75 (2-4)	2.71 (2-3)
7	2.50 (2-3)	2.64 (2-3)
8	2.34 (1-3)	2.71 (2-4)
9	2.17 (2-3)	2.64 (2-3)
10	1.92 (1-3)	2.29 (2-3)
11	1.50 (1-2)	1.64 (1-2)

*Questions using 6-point Likert scale with 1 indicating "strongly agree" and 6 indicating "strongly disagree." Differences between groups were not statistically significant.

took the rotation in the first part of the year or the second part of the year, an analysis of all three groups yielded the following results. As expected, those students participating in the second half of their third year performed significantly better on the pretest (*P* values ranging from .0002 to .014). As previously mentioned, data analysis of the pretest and posttest difference vs the pretest demonstrated a strong ceiling effect, especially in the students in the second half-year groups. Comparison of the amount of time spent completing either the assigned reading or the computerized tutorial did not demonstrate any significant differences between the first half-year and the second half-year students (group B, *P*=.265; group C, *P*=.433).

The students who participated in the microcomputer tutorial also appeared to have enjoyed the experience and found it useful (Table 2). On the acceptability index, most of the means of the 11 items ranged between "agree" and "slightly agree," with one item listed between "strongly agree" and "agree." This highest score was in response to the item, "This program improved my knowledge about well-newborn care." The lowest mean score was in response to the item, "The text was easy to understand" (mean, 2.73). There were no statistically significant differences between the two half-year subsets on the results of the acceptability index.

COMMENT

As has been demonstrated by a number of authors, CAI for medical education is an important tool and one that will probably have increasing importance in the future.[3,9] In this study, which is one of the few to evaluate a computerized medical tutorial, the results illustrate the effectiveness of presenting specifically selected basic information to teach students. This is extremely important in situations in which the time spent during the clinical experience (in this case, a well-newborn nursery) is very limited. Other medical educators such as Schreiner et al[10] have had medical students use audiovisual materials to try to more efficiently teach in the well-newborn nursery.[10]

It was a common practice in the past, and may still be so in some instances, to tell medical students at the beginning of a clinical rotation to read a particular textbook. However, they often do not receive any guidance about what specific information may be important for them to learn. In this study, both the students who completed specific selected readings and those who spent time with a microcomputer learning selected information did comparably well. Those students who had no guidance for their learning experience did not show much, if any, improvement. However, it remains a possibility that the control group (group A) learned information that was not reflected in the posttest results.

The most important result of this study is that demonstrated by the time spent by students completing either the assigned reading or the microcomputer tutorial. The computer group spent nearly 20 minutes *less* time than the reading group. Obviously, had the reading group only been given the textbook to read without any guidance regarding specific paragraphs and pages, the time spent by the reading group would have been much greater. These students were requested to only read the indicated parts and to keep track of the time spent reading these specific pages and paragraphs. It is likely, as some students later admitted, that many students later read more of the book than was required.

Although the amount of this serendipitous learning was not evaluated, it may well be that the reading group picked up more useful information in this way. Some of the students who performed the computer tutorial or the readings also later requested to be able to read the textbook or to do the tutorial. It is uncertain whether the learning of these students was somehow enhanced when they followed up either the computer tutorial with reading or the reading with the tutorial. The investigators were pleased, however, that some students had been motivated into wanting to learn more.

It is possible that there may be some unreliability in the time reports given by the students in groups B and C. Alternative study designs were considered in planning the study, such as having a program coupled to the CAI program that would keep track of the time or possibly the use of hand-held stopwatches supplied to all the students. These ideas were rejected primarily because they were believed to be more intrusive or expensive and still subject to most of the same errors that may occur with self-report methods (eg, the student could leave the computer on, but not be using the CAI program). Both groups were allowed to have stops and starts. Using the CAI program, as well as the textbook, allowed students to end at any of several places, leave for any period of time, and start again later where they left off.

The time differential between groups might have been less if additional effort had gone into organizing the reading material. Passages of text could have been highlighted or underlined or other guides developed. It would have also been possible to prepare a programmed text with interspersed questions to stimulate learning. However, the effort required to perform such tasks would have been nearly that required to prepare the CAI program. In addition, the students who would use such a guide may not do as well comparatively since using computers, perhaps because it is still a novelty, frequently appears to be an additional enticement to learning new material.[9]

The use of an authoring system to develop the CAI program expedited its creation and made it possible for persons other than computer programmers to prepare the lesson. It may well be the current, most appropriate, and cost-effective way of preparing medical instructional programs, as well as some types of patient treatment simulations. The use of authoring systems allows a person with only a basic understanding of computers to develop an effective instructional program. It also allows, as was done with our CAI program, an easy way to add site-specific information to the program, as well as allowing alterations of the tutorial to be made as knowledge about diseases or treatments changes.

The issue of cost-effectiveness is often raised when there is an assessment of CAI. This was a specific concern with the development of the CAI program for this study, as it was entirely self-supported. Our assessment of this was very favorable, in terms of both time and money spent. The computer tutorial is equivalent to about 2 hours of didactic lecturing, and thus saves about 44 hours of faculty time per year, not including any preparation time for the faculty person. In regard to monetary concerns, the tutorial was primarily developed by a medical student working about 30 hours per week for 10 weeks. This student was hired at a total cost of $1500 as part of a summer research fellowship. He was not versed in the use of the authoring program prior to beginning work, and some of the time initially spent was in learning the system. However, additional time will be required to improve the CAI program in response to the feedback from the students.

The authoring system costs about $600, although some optional modules were purchased that were not actually used for this particular CAI program. The microcomputers used by the students were within a large microcomputer area in the medical library and are used for multiple purposes. This type of facility is becoming more commonplace, which improves on the overall cost-effectiveness of producing or acquiring CAI in that the cost of purchasing microcomputer equipment does not have to be figured into the total cost for one specific project.

CAI medical tutorials should work well as preliminary lessons that might be followed up by patient treatment simulations. The improvement of software and hardware for microcomputers in general and, specifically, the refinement of authoring systems recently and in the future, will allow more medical educators to be able to prepare these computerized lessons locally. The main advantage of this will be that these tutorials and simulations are more likely to suit individual teaching needs.

Although this study had a somewhat small number of subjects, CAI programs appear to promise to be increasingly important in medical education. It is also evident that the use of medical CAI programs are currently not being fully exploited. Current events, and likely future situations, appear to indicate that there will be further erosion of the time that clinical medical educators can spend in teaching. This is primarily because of increasing demands put on them for direct patient care. It is important, therefore, that time-saving and cost-effective measures be developed to ensure that the teaching of medical students does not suffer. The further development of CAI programs for medical education may be one way that students can be assured of having an efficient and individualized learning experience.

The authors wish to thank Brad Robison, MD, for his assistance in the development of the CAI tutorial.

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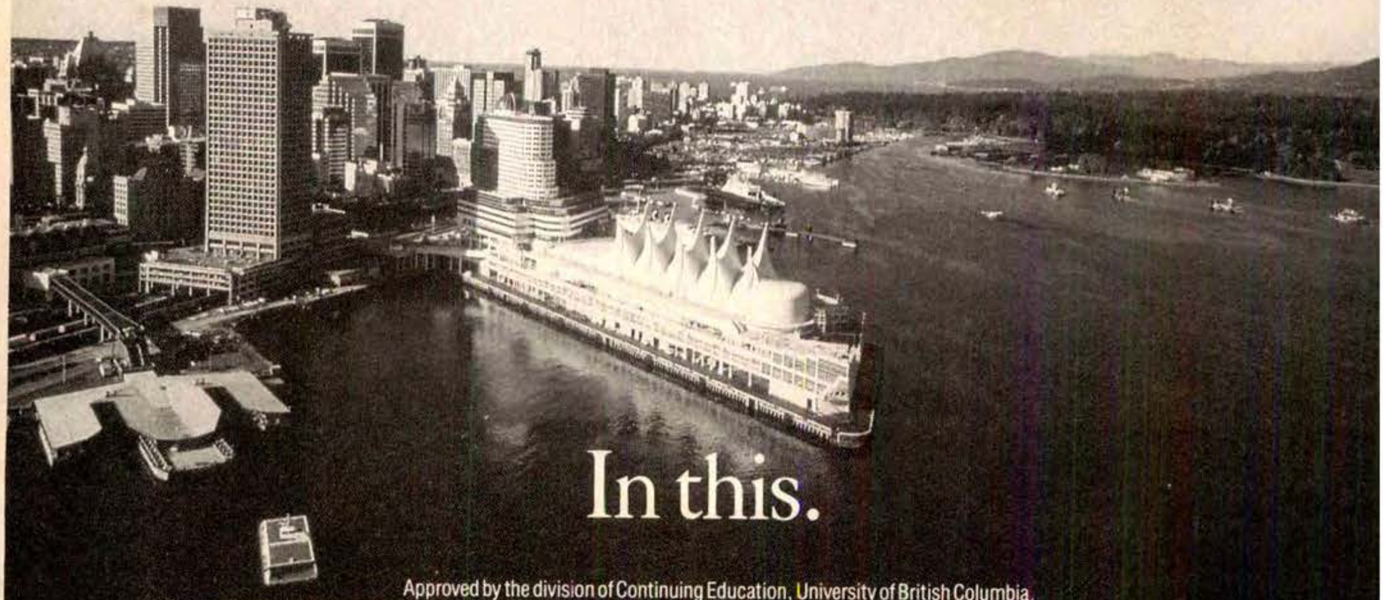

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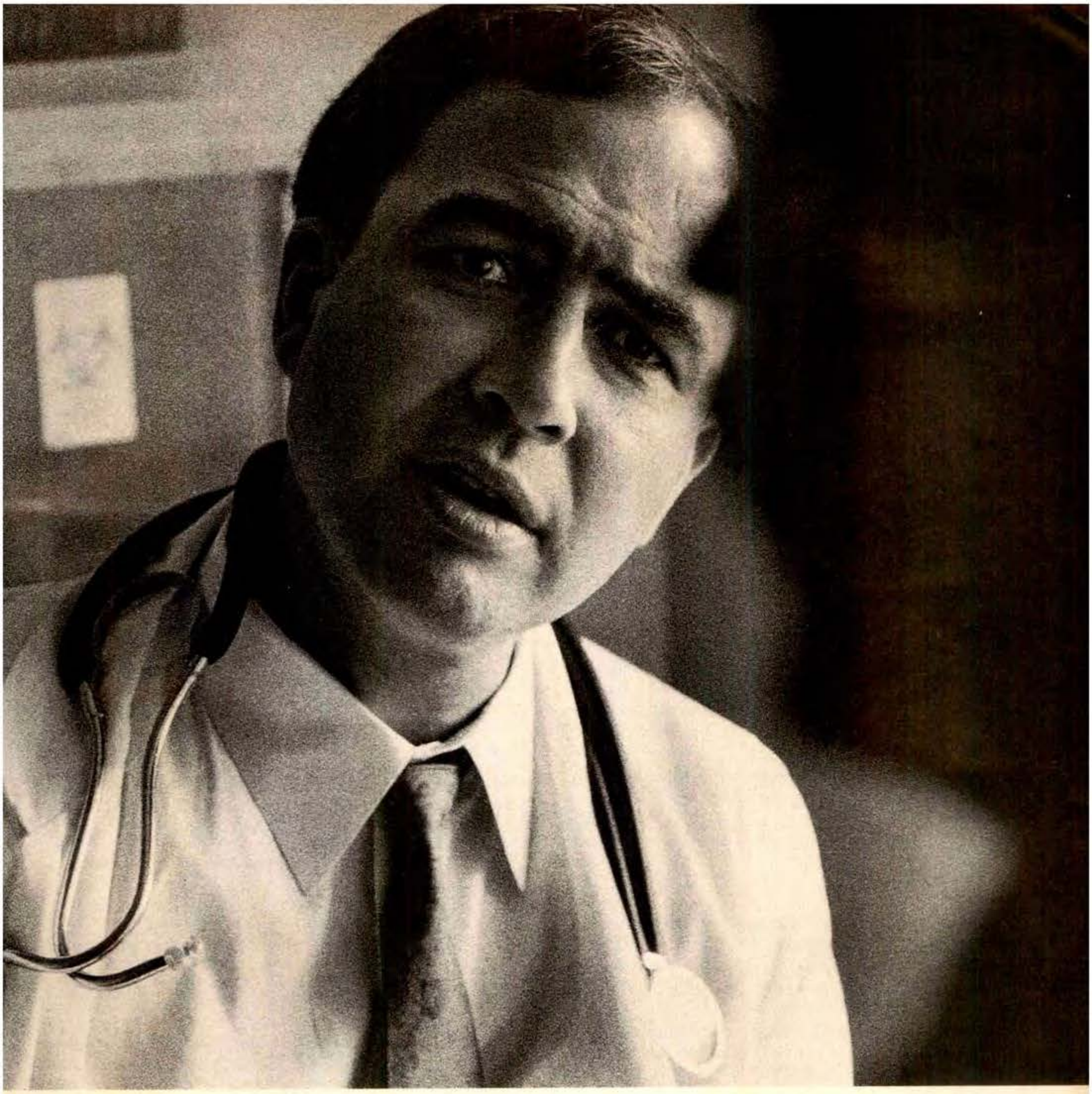

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Obesity Among Mescalero Preschool Children

Association With Maternal Obesity and Birth Weight

Margaret M. Gallaher, MD; Fern R. Hauck, MD, MS; Miranda Yang-Oshida, RD, MPH; Mary K. Serdula, MD, MPH

• **The prevalence of obesity among native American children ranks with the highest in the United States. However, little is known about associated risk factors for obesity among these children. We conducted a medical record review of 261 preschool children enrolled in the Mescalero Apache tribe to determine the prevalence of obesity and associated risk factors. The prevalence of obesity (weight for height >95th percentile) in this population was 19.5%. The prevalence of obesity (body mass index >95th percentile) in their mothers was 23%. Children with obese mothers were more than twice as likely to be obese than children of nonobese mothers. Children with a high birth weight were three times as likely to be obese as children of low or normal birth weight. The high prevalence of obesity may be due to both life-style and dietary patterns on the reservation. Family-based interventions are needed to prevent obesity and its long-term consequences in this population.**

(*AJDC.* 1991;145:1262-1265)

Obesity among children is increasingly recognized as a significant nutritional disorder that is linked to orthopedic problems, hypertension, and psychosocial difficulties.[1-6] In addition, obese children may be more likely to become obese adults[7,8] who are at additional risk of morbidity. Obese adults are often resistant to interventions[9]; therefore, preventive measures targeted at children may be more successful in forestalling the long-term consequences of this disorder.

Data from the Pediatric Nutrition Surveillance System demonstrate that native American children have a higher prevalence of obesity than either black or white children.[10] Although some studies of predominantly white and black preschool children have identified risk factors for obesity, such as familial obesity,[11,12] socioeconomic status,[11-14] and small family size,[15] little is known about such factors among native American preschool children. Because the nutritionist (M. Y.-O.) for the Mescalero Apache tribe was concerned that a high proportion of children attending the well-child clinic was obese, we conducted a medical record review to determine the true extent of the problem, and as a first step in developing interventions to prevent obesity.

SUBJECTS AND METHODS

This study was conducted on the Mescalero Apache Reservation, which is situated on 460 000 acres in south central New Mexico. The chief sources of income on the reservation are timber sales, cattle farming, and recreational facilities. The per capita income was $1500 in 1988. As of 1988, 2893 were enrolled as tribal members and 295 (13.1%) children were under age 5 years.[16]

All primary health care for tribal members is provided at the Indian Health Service Hospital (Mescalero, NM), the only medical facility on the reservation. The hospital's medical records contain inpatient and outpatient records, including well-child visits and school physical examinations. It is estimated that at least 90% of the preschool children attend the well-child clinic.[16]

For inclusion in the study, children had to meet the following criteria: (1) born on or after January 1, 1983; (2) enrolled as a tribal member; (3) seen for a well-child visit in 1987 or 1988; (4) were age 1 to 5 years at the time of the well-child visit; and (5) mother's chart was available for review. From the child's medical record, we collected information on age, sex, number of siblings, birth order, birth weight, weight and height at the most recent well-child visit, and whether the child attended Head Start (a federally funded preschool program for low-income children). We also reviewed the mother's medical record for information on her age at the time of the child's birth, her most recent nonpregnant weight and height, her marital status, and whether she had ever been diagnosed as having diabetes. We obtained the mother's employment status from the tribal office.

Because siblings tend to have similar physical characteristics, only one child per family was included in the analysis to eliminate potential bias. Children were included in the study by alternately selecting the older and the younger child in families with two children, and alternately selecting the oldest, middle, and youngest child in families with three children. No families had more than three children who met the study criteria.

Using the ANTHRO software program,[17] anthropometric indices (weight for height [W/H] and height for age [H/A]) were calculated based on the National Center for Health Statistics (NCHS) reference population.[18,19] We defined obesity among the children as W/H above the 95th percentile, underweight as W/H below the 5th percentile, and short stature as H/A below the 5th percentile. Obesity among the mothers was defined as body

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From the Division of Nutrition, Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control, Atlanta, Ga (Drs Gallaher, Hauck, and Serdula), and Mescalero Indian Health Service Hospital, Mescalero, NM (Ms Yang-Oshida).

Adapted from a presentation at the Epidemic Intelligence Service Conference, Atlanta, Ga, April 3, 1989.

Reprint requests to Division of Nutrition, Mail Stop K26, Centers for Disease Control, Atlanta, GA 30333 (Dr Serdula).

Age Distribution of Mescalero Apache Children and the Prevalence of Obesity in Children by Risk Factor

Risk Factor	No. (%) of Subjects	% Obese	Prevalence Ratio	95% Confidence Interval
Age of child, y				
5	20 (8)	20.0	0.9	(0.3, 2.3)
4	69 (26)	18.8	0.8	(0.4, 1.6)
3	49 (19)	18.4	0.8	(0.4, 1.7)
2	58 (22)	17.2	0.8	(0.4, 1.5)
1	65 (25)	23.1	1.0	Referent
Maternal obesity				
Yes	61	36.1	2.5	(1.6, 4.0)
No	200	14.5	1.0	Referent
Birth weight, g				
≥4000	36	36.1	3.0	(1.3, 6.8)
3000-3999	167	18.6	1.5	(0.7, 3.3)
2000-2999	58	12.1	1.0	Referent

mass index (weight divided by square of height) above the 95th percentile of women aged 20 to 29 years in the NHANESII reference population.[20]

The Epi Info computer program was used to calculate prevalence ratios (calculated in the same way as a relative risk) and 95% confidence intervals (CIs) for the prevalence ratios.[21] Variables significantly associated with obesity among the children by univariate analysis were further analyzed with logistic regression to determine the magnitude of their independent association with obesity.[22] Childhood obesity (present or absent) was the outcome variable in the logistic regression analysis. The magnitude and direction of the link between a child's obesity and the predictor variables were estimated by the odds ratio. Predictor variables included age (age 1 to 5 years), sex, birth weight (<3000 g, 3000 to 3999 g, or ≥4000 g), and maternal obesity (present or absent).

RESULTS

Of the 431 Mescalero children identified as meeting the age criteria, charts were located for 409 (95%). Of these, 377 preschool children had had a well-child visit in 1987 or 1988. Mothers' records were available and reviewed for 364 (97%) of the children. Excluding all but one child from each family left 261 children included in the analysis.

Fifty percent of the children were boys, eight (3%) had a birth weight below 2500 g, and 36 (14%) had a birth weight above 4000 g. Children aged 5 years made up the smallest proportion of the total study population (Table) because children receiving their last immunization at age 4 years would be discharged from the well-child clinic and would not return at age 5 years.

The overall prevalence of obesity among the children was 19.5% ($n=51$), which is significantly greater than the expected prevalence of 5% based on the reference population ($P<.000001$, binomial distribution). In contrast, 1% of the children were underweight and 6% had short stature. Of the mothers, 61 (23%) were obese.

Obese children were 2.5 times more likely to have an obese mother than nonobese children (Table). Prevalence of obesity increased with increasing birth weight. No association existed between obesity and the age or sex of the child, number of siblings, or birth order, nor were maternal employment, maternal diabetes, marital status, or age closely connected with this condition.

In the logistic regression model, childhood obesity was significantly associated with maternal obesity and birth weight after adjustments were made for age and sex of the child. The adjusted odds ratio of obesity for children whose mothers were obese was 4.8 times (95% CI, 1.8 to 12.8) higher than that of children whose mothers were not obese. The adjusted odds ratio of obesity for children with a birth weight above 4000 g was 4.4 (95% CI, 1.3 to 15.4).

Among infants born to obese mothers, 24% were of high birth weight (>4000 g) compared with only 11% of infants born to nonobese mothers (prevalence ratio, 1.93; 95% CI, 1.16 to 3.23). Because birth weight and mother's obesity are shown here and in other studies to be closely related, we examined for the presence of multicollinearity between maternal obesity and birth weight in the logistic regression model. First, no change appeared in the magnitude of the odds ratios or the CIs around the odds ratios when the logistic regression model contained either one or both of the variables. Second, we calculated the correlation between maternal body mass index and infant birth weight as continuous variables; a correlation (r) of .05 (95% CI, −0.07 to 0.17) indicates a correlation not sufficient to cause problems with multicollinearity in the logistic regression model.

COMMENT

Compared with data from the NCHS reference populations (which were predominantly composed of white and black children), the prevalence of obesity among Mescalero children and their mothers was greater than expected. The prevalence of short stature was as expected, whereas that of low weight was lower than expected. These findings are consistent with those of the Pediatric Nutrition Surveillance System, which used the same criteria to define obesity, although the prevalence of obesity from the Pediatric Nutrition Surveillance System was somewhat lower (8% to 13%) among native Americans than in our study.[10]

The NCHS reference population is probably not the ideal population with which to compare native American children, as the standard is composed of predominantly white and black children. Little is known of the body composition of native American children and how this may influence comparisons with other ethnic groups. In a study of Peruvian children, high W/H (compared with the NCHS reference population) was associated with lower body fat and greater lean tissue hydration.[23] Until an appropriate reference is developed for native American children, as well as children of other ethnicities, the NCHS standard will continue to be used because it is both well-known and accessible to clinical practitioners.

Previous studies have identified risk factors for obesity among other populations of children, including familial obesity,[11,12] high birth weight,[24,25] low or high socioeconomic status,[11-14] and small family size.[15] Of the risk factors examined in our study, maternal obesity and high birth weight were most strongly associated with childhood obesity. The relationship between the weight class of parents and that of their child is well documented, and some studies have shown a stronger association between the weight class of the mother and obesity in the child compared with the father's weight class.[24,25] A study of Mexican-American preschool children found that mothers of obese children preferred a fatter baby, were "pushier" feeders, and were more likely to be obese themselves.[26] Based on our record review, we cannot assess maternal attitudes and perceptions of the child's weight or determine the magnitude of the contribution of common environmental factors and genetic factors to the link between maternal and child obesity. It is probable that dietary factors and low physical activity contribute to the overall high prevalence of obesity.

Obesity among the children was closely related to high birth weight. Studies have shown that obese women tend to have children of higher birth weight,[27-29] and that children with high birth weight are more likely to remain taller and heavier than children of lower birth weight,[30] which could explain this finding.

We did not find an association between child obesity and maternal employment, the only measure of socioeconomic status available by chart review. The Ten State Nutrition Survey showed a direct association between socioeconomic status and the prevalence of obesity among preschool children.[11] Other studies, which examined white preschool children only, found the opposite—that obesity was inversely related to socioeconomic status.[12,13] This population of native Americans may be too small and too homogeneous to detect differences in obesity due to socioeconomic status. Further studies are needed to clarify this issue among this and other native American populations.

In this study, W/H was chosen as the measure of obesity because it is the most practical and widely used and can be abstracted from existing medical records. Obesity, defined as an abnormally high proportion of body fat, can only be approximated by anthropometric measurements. The correlation between high W/H and obesity may be low among young children.[31] Weight for height cannot indicate whether increased weight is due to adiposity, increased muscularity, or edema. It is not known if the higher W/H in this population of native American children is due to an increase in body fat or a difference in body proportions. By defining obesity as W/H above the 95th percentile, we chose a definition that was extreme and, therefore, less likely to misclassify children as obese.

The strength of using record review in this population is that there is a single source of medical care, and attendance at the well-child clinic is high. However, there are several limitations to using a medical record review to determine risk factors for obesity. First, important contributing factors such as physical activity, diet composition, and the perception of the child's weight are not available from the medical record. Second, we did not have any information on the fathers of these native American preschoolers. Third, some degree of uncertainty was introduced by using charted measurements whose accuracy cannot be confirmed. However, we have no reason to believe that systematic measurement bias was operating during this study. Despite these limitations, the record review is a valuable first step in determining a baseline prevalence of and risk factors for obesity.

Further studies are needed to identify other potential risk factors for obesity to develop effective prevention strategies. The high prevalence of obesity among native American adults, with its associated high rates of diabetes and hypertension, is well documented.[32] Interventions are needed that focus on preventing obesity during childhood to avoid the long-term consequences of obesity in this population. Preschool children may be a desirable target population because they have regular contact with the medical system during well-baby visits. Given the high prevalence of obesity among the mothers and the strong association between child and maternal obesity, interventions targeted at the family rather than just the child may be most effective.

The opinions expressed in this article are those of the authors and do not necessarily reflect the views of the Indian Health Service.

The authors thank the Tribal Council, the record room staff at the Mescalero (NM) Indian Health Service Hospital, Robert Baldor, MD, and the Albuquerque (NM) Area Indian Health Service Office for their assistance in conducting this study.

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Monozygotic Twins With Seizures: Shared Characteristics

Rosalind A. Segal, Md, PhD; Catherine Chapman, MD; John Barlow, MD (*Arch Neurol.* 1991;48:1041-1045)

Isolated Congenital Hemianopia Caused by Prenatal Injury to the Optic Radiation

Nicola K. Ragge, MRCP, FCOphth; A. James Barkovich, MD; William F. Hoyt, MD; Scott R. Lambert, MD (*Arch Neurol.* 1991;48:1088-1091)

Serum Lipid Concentrations in Subjects With Phenylketonuria and Their Families

Terry J. DeClue, MD; Jim Davis, MD; Dawn M. Schocken, MPH; Ruth Kangas, RD; Steve A. Benford

• To determine if subjects with phenylketonuria receiving diets significantly lower in cholesterol and saturated fat had serum lipid concentrations different from those of their family members, we measured serum concentrations of total cholesterol, high-density lipoprotein cholesterol, and total triglycerides in the probands with phenylketonuria, their parents, and their siblings. Eleven adults (seven women and four men) and 16 children (eight girls and eight boys) were studied. Ten subjects (four girls and six boys) had phenylketonuria. Subjects with phenylketonuria consumed less cholesterol (0.02 vs 0.41 mmol/d) and fat (median, 21% vs 39.5% of total calories), and their diets had a higher ratio of polyunsaturated to saturated fatty acids (median, 2.0 vs 0.2) than did their siblings without phenylketonuria. The diet of the parents was similar to that of their offspring without phenylketonuria. No differences were noted between the subjects with phenylketonuria (consuming a diet lower in saturated fat and cholesterol) and their siblings without phenylketonuria in serum concentrations of total cholesterol (median, 3.34 vs 3.07 mmol/L); high-density lipoprotein cholesterol (median, 1.44 vs 1.37 mmol/L); low-density lipoprotein cholesterol (median, 1.44 vs 1.09 mmol/L); or triglycerides (median, 0.89 vs 0.54 mmol/L). We conclude that previously reported lipoprotein abnormalities noted between unrelated subjects with and without phenylketonuria may not be due to differences in dietary intake, but rather due to a (genetic) predisposition of the population with phenylketonuria toward lower serum lipid concentrations.

(*AJDC.* 1991;145:1266-1268)

Phenylketonuria (PKU) is an inborn error of metabolism secondary to a deficiency of phenylalanine hydroxylase. It is inherited as an autosomal recessive trait, and dietary intervention is the only treatment currently available. The basis of the PKU diet is to restrict phenylalanine intake early in life. To supply the recommended daily allowances of protein, carbohydrates, and fats, special casein hydrolysate formulas are used. As the patient ages, various low-protein solid food exchanges are added to the diet. Because of the reduction of animal protein in the patients' diet, they generally consume a lower percentage of calories from fat and cholesterol than does the general population.[1,2] It has been suggested that the PKU diet is responsible for the lower values of total cholesterol, low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) noted in the subject with PKU.[1-3] We evaluated lipoproteins in children with PKU and their families to determine if other (familial) factors might be responsible for these changes in serum total cholesterol.

SUBJECTS AND METHODS

Seven families with at least one child attending the PKU clinic at the University of South Florida were enrolled. Ten children (four girls and six boys) with PKU (median age, 7.3 years; range, 0.75 to 30 years) and six siblings without PKU (two girls and four boys; median age, 7.1 years; range, 5 to 17 years) were evaluated. Two subjects with PKU were older than 25 years (27 and 30 years) and had not been prescribed a phenylalanine-restricted diet at birth. At the time of the study, all subjects with PKU were receiving an appropriate phenylalanine-restricted diet. Eleven parents (seven women and four men) with a median age of 33 years (range, 24 to 48 years) were also studied. All subjects were euthyroid and none was obese. The study was reviewed and approved by the Institutional Review Board of the University of South Florida; informed consent was obtained from each family member before enrollment. Each subject studied completed a 3-day food diary before blood collection. The food diary was analyzed by a registered dietitian using Nutritionist III (N-Squared Computing, Silverton, Ore) for content of protein; carbohydrate; fat; cholesterol; and monounsaturated, polyunsaturated, and saturated fatty acids. The dietary information for each individual was averaged and reported as median and range for a 24-hour period.

On the day of blood collection, following an overnight fast, the subjects' heights and weights were measured and they were allowed to sit for 10 to 15 minutes before blood samples were collected through an antecubital vein. Following collection, the serum was separated immediately. Serum concentrations of total cholesterol, HDL-C, triglycerides, and thyrotropin were measured in all subjects, and phenylalanine levels were determined in the probands with PKU. The serum sample for HDL-C was refrigerated at 4°C until assayed 48 to 72 hours after collection. Serum samples for analysis of total cholesterol, triglycerides, and thyrotropin were frozen at −70°C until assay. Total cholesterol, HDL-C, and triglyceride levels were measured at the University of Miami using nationally standardized methods previously de-

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Reprint requests to University of South Florida, MDC Box 45, 12901 Bruce B. Downs Blvd, Tampa, FL 33612-4799 (Dr DeClue).

Table 1.—Dietary Analysis of Children With Phenylketonuria (PKU) and Their Family Members*

		Median (Range)				
Subjects	**No. of Subjects**	**Protein**	**Carbohydrate**	**Fat**	**Cholesterol, mmol/d**	**P/S Ratio**
Parents	8	20 (15-29)†	41.5 (28-63)†	38.5 (15-54)‡	0.63 (0.16-3.63)	0.59 (0.1-1.3)†
Children with PKU	7	11 (8-16)	68 (50-79)	21 (9-41)	0.02 (0.002-0.12)	2.0 (0.94-3.7)
Non-PKU children	4	15 (13-21)‡	46 (38-49)†	39.5 (38-42)†	0.41 (0.37-0.56)	0.2 (0.15-0.57)†

*Protein, carbohydrate, and fat values are percentages of total calories consumed per day. P/S indicates ratio of polyunsaturated to saturated fatty acids.

†$P<.005$ for children with PKU vs parents or non-PKU children.

‡$P<.05$ for children with PKU vs parents or non-PKU children.

Table 2.—Serum Lipid Concentrations*

		Median (Range)			
Subjects	**No. of Subjects**	**Total Cholesterol mmol/L**	**HDL-C, mmol/L**	**LDL-C, mmol/L**	**Triglycerides, mmol/L**
Parents	11	5.15 (2.96-6.63)	1.53 (0.78-3.12)	3.15 (0.42-4.73)	0.89 (0.15-2.40)
Children with PKU	10	3.34 (2.76-4.42)	1.44 (0.91-2.34)	1.44 (0.18-2.78)	0.89 (0.32-1.61)
Non-PKU children	6	3.07 (1.79-4.03)	1.37 (1.09-2.26)	1.09 (0.16-2.18)	0.54 (0.25-1.33)

*HDL-C and LDL-C indicate high-density and low-density lipoprotein cholesterol, respectively.

scribed.[4] Thyrotropin level was measured with a standard radioimmunoassay. Serum phenylalanine was measured using ion exchange chromatography with postcolumn triketohydrindene hydrate (Ninhydrin) detection. Statistical analyses were made using Student's *t* test.

RESULTS

The patients with PKU consumed significantly fewer calories from total fat and protein, but more calories from carbohydrates, than did their family members (Table 1). The subjects with PKU also consumed significantly less cholesterol in their diet, and the ratio of their polyunsaturated to saturated fatty acid intake was much higher. The diet of the parents was similar to that of the siblings without PKU; although the parents consumed more cholesterol, the difference was not statistically significant.

No differences were noted in serum concentrations of total cholesterol, HDL-C, LDL-C, and triglycerides between the subjects with PKU (consuming a diet significantly lower in cholesterol and higher in polyunsaturated fat) and their family members (Table 2). The serum concentrations of total cholesterol, LDL-C, and triglycerides in the parents were higher, but not statistically different, from the offspring with or without PKU. The HDL-C values were similar among all three groups. Thyrotropin levels were normal in all subjects. The mean (±SD) serum phenylalanine concentration in the patients with PKU was 365±242 μmol/L.

COMMENT

Previous investigators have reported that serum or plasma total cholesterol values were significantly lower in subjects with PKU than in unrelated control subjects without PKU.[1-3] Acosta et al[3] evaluated 93 children with PKU (23 children were not receiving a phenylalanine-restricted diet) and 30 normal control subjects and found that the total and free serum cholesterol values were lower in the children with PKU than in the normal subjects. Galluzzo et al[2] measured plasma levels of total cholesterol and HDL-C in 40 healthy, treated patients with PKU (triglycerides were measured in 30) and 150 sex- and age-matched control subjects. In this study, patients with PKU had significantly lower total cholesterol values than control subjects. There was no difference in HDL-C or triglyceride values, and LDL-C levels were not determined. Similarly, Schulpi and Scarpalezou[1] evaluated serum lipid concentrations in 20 Greek children with PKU and compared them with those in 200 matched healthy children. Significant differences were noted in triglyceride, total cholesterol, HDL-C, and very low density lipoprotein cholesterol concentrations, with the subjects with PKU having the more favorable profile. There was no difference in LDL-C levels between the two groups.

Recently, it has been noted that there is genetic heterogeneity in the response of serum lipid concentrations to alterations in the intake of cholesterol and saturated fat.[5] Sensitivity to dietary cholesterol varies among subjects, with the majority effectively compensating for increases in dietary cholesterol by feedback suppression of endogenous cholesterol synthesis, coupled with a reduction in dietary cholesterol fractional absorption. Hypothesizing that familial factors in addition to diet may affect serum lipid concentrations in individuals with PKU, we evaluated subjects with PKU and compared them with their parents and siblings without PKU.

Our study confirms that individuals with PKU receiving an appropriately low-phenylalanine diet consume significantly less cholesterol and a lower percentage of calories from fat in their diet. The majority of the fat consumed by our children with PKU consisted of polyunsaturated fatty acids. Diets high in polyunsaturated fatty acids lower HDL-C in subjects without PKU; however, no differences were noted in our study in HDL-C levels between groups. The small number of patients in this study does not reveal subtle changes that might occur in HDL-C between the various groups.

The greatest differences among the two sibling groups was between serum concentrations of total cholesterol and HDL-C and total triglycerides. It is interesting that those children (without PKU) who consumed the largest amount of cholesterol and saturated fatty acids in their diet had lower serum total cholesterol and LDL-C concentrations. This is contrary to what one might expect since subjects consuming the highest amounts of dietary cholesterol are expected to have the higher serum total cholesterol concentrations. It is unlikely that age-related differences could account for the differences in serum cholesterol measurements between the siblings with and without PKU, since the subjects with PKU were of similar age. If the two oldest subjects with PKU are excluded in the analysis, the results are essentially the same (serum total cholesterol [$n=8$]: median, 3.46 mmol/L; range, 2.8 to 4.5 mmol/L). In view of this finding it is possible that the serum total cholesterol changes noted during variations in dietary intake are related to a threshold effect. For example, within genetically similar groups, unless a quantity of cholesterol above a certain threshold is consumed, the serum total cholesterol is unchanged. This would be in agreement with the findings of McNamara et al.[5]

Higher serum triglyceride values in children with PKU have been reported previously and have been suggested to be secondary to the significantly higher percentage of calories from carbohydrates consumed by the subject with PKU.[1] We noted similar findings in our study and agree that increasing the total percentage of calories from fat in the form of monounsaturated fatty acids in the diet (and lowering the polyunsaturated fatty acids and carbohydrates) may have a more favorable effect on serum HDL-C and LDL-C concentrations, as well as on serum triglyceride measurements.[6]

As a group, the families with PKU have favorable lipid profiles (Table 2). Of the seven families studied, one had familial combined hyperlipidemia. The proband with PKU was the only child in this family. Compared with the other siblings (with or without PKU), this child had the highest serum total cholesterol (4.4 mmol/L) and LDL-C (2.8 mmol/L) values. If this family is excluded from the analysis, there is no significant change in the overall results.

Subjects with PKU consume a diet that is less atherogenic than that of the general population. Previous studies have compared lipid profiles in children with PKU (demonstrating lower total cholesterol concentrations) to unrelated normal children without PKU.[1-3] It is likely that those studies were flawed in their comparisons because they did not control for possible genetic influence in cholesterol metabolism between the two groups. We did not demonstrate any differences in serum total cholesterol levels between children with or without PKU, although the subjects without PKU consumed 10 times more cholesterol and twice the fat in their diet. The highest total cholesterol and LDL-C measurement among the siblings studied was in a child with PKU from a family with familial combined hyperlipidemia. If the serum total cholesterol data from these children with PKU had been compared with data from children from the general population, the wrong conclusion would have been made (ie, that the lower cholesterol and fat in the diet is responsible for the lower serum total cholesterol values in the subjects with PKU). Our study suggests that genetic influences in cholesterol metabolism should be considered an important variable in interpreting total cholesterol data from children. Our data suggest that families with a child with PKU have lower serum total cholesterol values than the general population and that other factors (eg, familial combined hyperlipidemia) have a greater influence on cholesterol metabolism than diet.

We wish to thank Ronald Goldberg, MD, for measuring the lipoproteins, and Herbert H. Pomerance, MD, Allen W. Root, MD, and John I. Malone, MD, for their critical review of the article.

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Adolescent Pelvic Examination

An Effective Practical Approach

Hyman C. Tolmas, MD

• The American Academy of Pediatrics has recommended that pediatric health care be extended through the adolescent years. Thus, there is a need to refamiliarize the physician with the pelvic examination. Formerly, workshops used simulated plastic models ("Ginny") to accomplish this goal. Such workshops have been conducted at the annual meeting of the American Academy of Pediatrics for several years. At the 1987 meeting in New Orleans, La, two workshops involving live models (gynecologic teaching assistants) were planned and implemented with great success. Following a didactic segment, each participant was given an opportunity to perform the pelvic examination with immediate feedback from the gynecologic teaching assistant as to the completeness and appropriateness of the pelvic examination. The immediate response of the attendees was overwhelmingly positive. A questionnaire was sent to the enrollees 8 months after the meeting to determine whether this experience had affected their attitude toward and approach to the pelvic examination. Eighty-three percent of questionnaires were returned with an affirmative response. This positive response suggested that such workshops be continued in an effort to reach as many pediatricians as possible.

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For several years, the Adolescent Health Section of the American Academy of Pediatrics has conducted workshops at the annual meeting that used the plastic "Ginny" models to teach the correct methods to perform a pelvic examination. Videotapes demonstrating the technique were used, and one or more moderators assisted participants with their examinations and answered questions.

The academy has placed special emphasis on adolescent health care.[1] Thus, pediatricians must learn or relearn how to perform pelvic examinations on adolescent patients. The gynecologic examination of an adolescent should not be a difficult experience for the patient, the parent, or the physician. The skills necessary to ensure a successful examination are attainable by any sensitive pediatrician willing to take the time to acquire them.[2] Historically, instruction in performance of the abdominal/pelvic examination in medical school and residency programs has been neglected. The objective of this workshop was to familiarize the pediatrician with the special needs of the adolescent gynecologic patient and to make him or her feel at ease while performing a screening examination of the female genitalia.

The use of live human models to teach the pelvic examination was originally introduced at a few medical centers beginning in 1971. Kretzschmar[3] reported his experience at the University of Iowa, Iowa City, employing trained volunteers called gynecology teaching associates (GTAs) to teach pelvic and breast examinations to medical students. This program proved to be an extremely effective method. Johnson[4] evaluated the impact of a similar system for a small group of students. The American Academy of Pediatrics first used the live teaching model at its annual meeting in 1986. Holzman et al[5] showed that students trained by professional simulated patients rated substantially better in psychomotor and interpersonal relations than did those taught by the mannequin or the physician preceptors techniques.

I presented the results of a carefully planned, hands-on workshop at the annual meeting of the American Academy of Pediatrics in 1987. I also presented the long-term effect as determined by questionnaire survey of the participants.

METHODS

Setting and Equipment

An appropriate setting is essential for adequate, "real-life" simulation of the examination milieu. Accordingly, the gynecologic clinic at Tulane Medical Center, New Orleans, La, was selected with provision of clinical examining rooms approximating the office setting of participants. In addition, classroom space was made available for the didactic sessions.

An adequate amount of supplies were provided for each examining room, eg, disposable gloves, specula, a mirror for patient education, a washbasin, laboratory equipment for the demonstration of Papanicolaou smears, and vaginal and cervical culture material for the preparation of microscopic slides. Visual aids were employed to explain pertinent concepts and to review anatomic relationships. A GTA acted as the overall moderator and supervisor for all the enrollees; she circulated among all examination sites.

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From the Department of Pediatrics, Tulane University School of Medicine, New Orleans, La.

Reprint requests to 466 Crystal St, New Orleans, LA 70124 (Dr Tolmas).

Table 1.—Results of Evaluation by Participants*

Category	Score, Session 1/Session 2
Overall evaluation	4.63/4.64
Relevance to practice	4.57/4.64
Appropriateness of topic	4.63/4.76
Discussion	4.34/4.60
Handouts	4.41/4.52
Audiovisual	4.36/4.36

*Each session is evaluated on a scale of 1 to 5, with 5 being the highest score. The categories of evaluations and the scores received for each session are listed.

Faculty

Three physicians presented the didactic material. Two of these physicians were gynecologists, and the third was a physician trained in adolescent medicine.

Program

The 40 physicians were divided into two groups. One group attended lectures by faculty. Each of the three speakers presented a 15-minute discussion on one aspect of adolescent gynecology, eg, preliminary examination, sexually transmitted diseases, and sexuality. A question-and-answer period followed the discussion.

The second group was divided into smaller groups of four for instruction by the GTA in an examination room. Details of the pelvic examination were demonstrated, and each attendee performed an examination of a GTA. Several diagnostic studies (eg, wet mount) were also performed. The groups then switched; those who had been in the lectures performed examinations and vice versa.

A kit consisting of informative material was provided to each participant and included a group of published articles relating to adolescent gynecology.[6] Also distributed was a brief summary of the Gynecological Teaching Associates Program, a flow chart about contraceptive measures, and a detailed chart about oral contraceptives.

EVALUATION

The American Academy of Pediatrics distributed an evaluation form usually used as a yardstick to determine the effectiveness of any given workshop or seminar. We developed a specific questionnaire to evaluate certain aspects of the workshop.

The American Academy of Pediatrics received 38 responses to 40 questionnaires sent for the morning session and 25 responses to 26 questionnaires sent for the afternoon session. The ratings of the participants are listed in Table 1.

Among the comments by both session participants in response to a question about the most helpful aspects of the workshop were the following: "the hands-on experience," "graduate teaching assistants to teach the performance of the pelvic examination and actually performing the examination," "practicality and suitability for practice," "organization," "how to approach the adolescent patient and what to tell her," and "the discussion about the sexually abused child."

Among those comments listed in response to a question about the least helpful aspects of the workshop were as follows: "too many lectures in a short time," "lack of time," "too hurried," "should have more time for lectures," and "lectures should precede the practical examination."

Table 2.—Ratings of 55 Respondents (of 66 Attendees) Listed by Category*

Category	Score
Usefulness of workshop	9.3±0.99
Clarity and effectiveness of instructors	9.1±1.12
Material covered	8.9±1.13
Value of take-home kit	8.9±0.97
Effect on your practice	8.7±1.27
Value of gynecologic teaching assistant	9.8±0.54
Usefulness of doing actual vaginal examination	9.6±0.86

*Scores are mean ± SD, with 10 being the highest score and 1 being the lowest.

Table 3.—Results of Follow-up Questionnaire

	Response, No. (%)	
Question	Yes	No
Were you performing pelvic examinations on your adolescent patients where indicated before attending the workshop?	33 (70.2)	14 (29.8)
Do you feel more at ease doing a pelvic examination on your adolescent patients now?	44 (93.7)	1 (2.13)*
Do you discuss sexuality with your female adolescents?	38 (80.85)	5 (10.64)†
Do you perform cultures and/or Papanicolaou smears?	43 (91.49)	3 (6.38)‡
Do you believe that this type of workshop should continue to be a part of the annual meeting?	47 (100)	0 (0)

*Two respondents (4.26%) did not answer.
†Four respondents (8.51%) answered "sometimes."
‡One respondent (2.13%) did not answer.

The respondents suggested that the course be extended to a 3-hour format. The results of the evaluation are listed in Table 2.

The comments were generally positive (eg, "excellent workshop," "hands-on experience invaluable," "feel comfortable with live models," and "should be required in medical school"). However, the most frequent criticism was inadequate time. A few participants suggested that the didactic lectures lacked sufficient specifics regarding birth control, sexually transmitted diseases, relating to parents of teenagers, and the psychological aspects of sexuality. The GTAs received the most positive comments (eg, "excellent," "extraordinary teaching skills," and "the most useful lesson I have learned").

FOLLOW-UP RATINGS

In June 1988, a follow-up letter and questionnaire were sent to the participants in the adolescent pelvic examination workshop requesting that they be completed and returned. Of the 70 questionnaires sent, 47 (67%) were returned with the results shown in Table 3.

RESULTS

Of the 47 respondents, 37 were pediatricians in private practice (26 were in group practice, and 11 were in solo practice). The other 10 respondents were distributed as follows: pediatric child abuse (n = 3), pediatric emergency room (n = 1), family practice (n = 1), resident in pediatrics (n = 1), college health (n = 2), and school health (n = 2).

In response to the question, "Identify the type of setting for patient care" (eg, school health, private practice, and community clinic), the following answers were recorded: private practice (n = 26), community clinic (n = 6), multispecialty group (n = 5), community/school health (n = 2), sexual abuse clinic (n = 2), large prepaid health plan (n = 2), and hospital (n = 4). Thirty-one answered affirmatively to the question "Do you perform pelvic examinations now?"

COMMENT

Gynecologic and contraceptive needs of teenagers were topics pediatricians had little need to consider in the past. Today, the pediatrician cares for a broader age group than in the past, necessitating knowledge and skills appropriate to this age group.[7,8] Learning the skills to perform the pelvic examination by the use of various plastic models of the breast, abdomen, and pelvis is inadequate. Plastic materials lack realistic pliability and resilience and the capacity for feedback about the accuracy of the examination. They also provide no sense of the potential discomfort that a patient may experience during the examination.[9]

An important component to adolescent gynecologic evaluation is the history obtained before the pelvic examination is performed. This should include family history; peer, school, and community involvement (social activities); and history of sexual activity and menstruation.

The first gynecologic examination is often of considerable importance for the female adolescent. She may feel pride, with a certain regret that she is leaving childhood behind. With sensitivity and careful planning, the physician will set the stage for a good physician-patient relationship that continues into adulthood.[10]

The program described herein, which utilizes live examinees, has been successful in refamiliarizing physicians with the need for pelvic examinations and ease with which they can be performed in the adolescent patient as judged by the positive responses of participants. There is a genuine need for evaluation procedures to measure the persistence of the learned skills and the adequacy of examinations in the actual practice of pediatric adolescent medicine.

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In Other AMA Journals

ARCHIVES OF OTOLARYNGOLOGY—HEAD & NECK SURGERY

The Role of Surgery in Rhabdomyosarcoma of the Head and Neck in Children

Gerald B. Healy, MD; Joseph Upton, MD;
Peter McL. Black, MD; Nalton Ferraro, MD, DMD
(*Arch Otolaryngol Head Neck Surg.* 1991;117:1185-1188)

Current Trends in Pediatric Residency Training

Carol Carraccio, MD, Alice Ackerman, MD

• A spreading gap has developed between available pediatric level 1 positions and those filled through the National Resident Matching Program. To define which variables enhance a program's ability to match, we surveyed program directors of all categorical pediatric training programs. An 82% response rate showed that ability to match was positively associated with larger program size and offering of shared residency positions. A negative association was found between many benefits and ability to match. The call schedule and number of call-free elective months had no measurable effect. Factors that we were unable to investigate, such as geographic location and academic reputation, may also play a role. Our results emphasize the irrelevance of enhancing benefits as a way of making programs competitive. Our energies need to be directed at attracting junior medical students to a career in pediatrics rather than competing for fourth-year students applying to pediatric programs.

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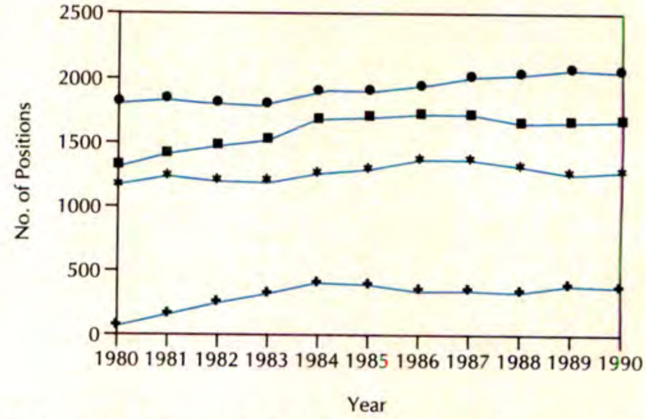

Fig 1.—*Positions available and filled by US (asterisks) and foreign medical graduates (pluses) through the National Resident Matching Program between 1980 and 1990. Plain line indicates positions available; line with squares, total filled.*

During the last decade, the total number of pediatric residency positions offered through the National Resident Matching Program (NRMP) has increased steadily from 1808 in 1980, to 2068 in 1989, with a slight drop to 2052 in 1990 (Fig 1).[1,2] Although the percent of US graduates applying for these positions has remained constant, ranging from 9.2% to 10%, the absolute number of US graduates in the matching program showed a steady increase only through 1985, with a gradual decline from 1986 through 1990.[1,2] During the early 1970s, approximately 8500 active US students were participating in the match, with a continued increase to a peak of 14 849 in 1985. A gradual decline then ensued, with only 13 908 US seniors actively participating in the 1990 NRMP.[1,2] The spreading gap created by the increasing availability of positions and the declining number of US graduates filling these positions has led to more programs not filling through the NRMP. In 1986, 135 (65%) of the 209 categorical pediatric training programs participating in the NRMP completely filled all their available positions.[3] In 1987, this figure dropped to 61%.[4] In 1988, 1989, and 1990, 52%, 41%, and 53% of programs, respectively, completely filled through the NRMP.[5-7]

Between 1986 and 1990, the percent of the total positions filled by US graduates fell from 86.1% in 1986, to 80.0% in 1989, rising slightly in 1990, to 81.3%.[1,2] During each of the last 5 years, foreign medical graduates filled 15% to 20% of the total number of pediatric positions filled through the NRMP. The current situation has created a competitive climate among programs to attract applicants to fill pediatric residency training positions. We undertook this study to determine which factors, if any, contribute to the ability of programs to fill their available positions.

Department Editors.—*Hugh D. Allen, MD, Columbus, Ohio; Fredric Burg, MD, Philadelphia, Pa; Harold Levine, MPA, Galveston, Tex; Barbara Starfield, MD, Baltimore, Md; Larrie W. Greenberg, MD, Washington, DC.*
Purpose.—*This department is intended to share information concerning educational efforts in the broad field of pediatrics. We welcome studies on the following topics: undergraduate and graduate education in medicine and allied health occupations; continuing education of health professionals; education of patients and families; and health education for the general public, the community, and organizations that contribute to the promotion and improvement of the health of children.*

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From the Department of Pediatrics, University of Maryland Medical Center, Baltimore.

Reprint requests to Department of Pediatrics, Room N5W56, University of Maryland, 22 S Greene St, Baltimore, MD 21201 (Dr Carraccio).

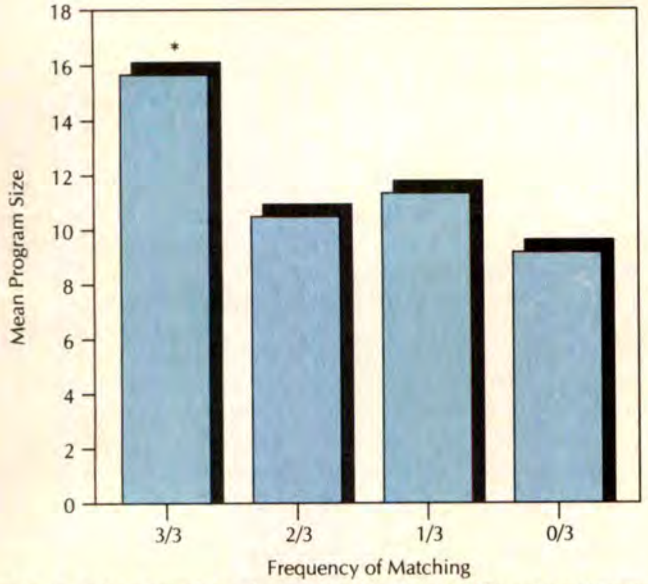

Fig 2.—*Mean number of pediatric level 1 positions in programs matching 3, 2, 1, or 0 of 3 years, 1987 through 1989. Asterisk indicates P<.05.*

MATERIALS AND METHODS

The 239 categorical pediatric residency training programs listed in the *1989-1990 Directory of Graduate Medical Education Programs*[8] were surveyed. We did not survey the 81 medicine-pediatrics, nine primary pediatrics, or two pediatrics-psychiatry–child psychiatry programs.[2] An anonymous questionnaire was sent to each program director requesting the following information: (1) total number of pediatric level 1 (PL1) positions; (2) whether the program matched for 1987, 1988, and 1989; (3) how many positions are reserved to be filled outside the NRMP; (4) the benefit package offered; (5) the frequency of night call in 1987, 1988, and 1989; (6) the number of shared residency positions; (7) the number of call-free elective months; and (8) the percent of male and female residents for each of the 3 study years. A second survey was sent to all programs 2 months after the first survey requesting program directors to respond if they had not previously done so.

The results were analyzed using Statistical Analysis Systems software. The data were separated into the following four groups for analysis: (1) those programs not filling their available positions in 1987, 1988, and 1989; (2) those programs filling 1 of the 3 years; (3) those programs filling 2 of the 3 years; and (4) those programs filling all available positions all 3 years. Analysis of variance and Tukey's test were used to determine whether significant differences in interval level variables existed among the groups. To analyze differences in categorical variables, the group matching 0 of 3 years was used as the reference, and all other groups were compared with it using a logistic regression model. We considered $P<.05$ to be significant.

RESULTS

One hundred fifty (63%) program directors responded on the first mailing. An additional 47 responded on the second mailing, for a total response rate of 82%.

Forty-five programs (23%) did not fill their available positions in the 1987, 1988, or 1989 NRMP. Forty programs (20%) filled all their positions 1 of 3 years, 37 (19%) filled 2 of 3 years, and 53 (27%) filled their positions 3 of 3 years. The remaining 11% either did not complete this information or indicated that they did not participate in the NRMP.

Fourteen percent of program directors, despite participation in the NRMP, reserved positions to be filled outside of the matching process. Further breakdown of the data showed 11% of those programs matching 0 of 3 years, 20% matching 1 of 3 years, 14% matching 2 of 3 years, and 8% matching 3 of 3 years in the reserved positions. Four percent of respondents did not answer this question.

Number (Percent) of Pediatric Programs Offering Various Benefits

	Years Matching			
Benefit	**0/3**	**1/3**	**2/3**	**3/3**
Medical malpractice	45 (100)	40 (100)	37 (100)	53 (100)
Medical insurance	41 (91)	40 (100)	36 (97)	53 (100)
Dental insurance	34 (76)	30 (75)	25 (68)	40 (75)
Life insurance	38 (84)	31 (77)	23 (62)*	37 (70)
Disability	30 (67)	29 (72)	25 (68)	44 (83)
Vacation	45 (100)	40 (100)	37 (100)	53 (100)
Conference funds	42 (93)	30 (75)*	29 (78)	33 (62)†
Parking	41 (91)	28 (70)*	26 (70)*	25 (47)‡
Meals	33 (73)	34 (85)	32 (86)	42 (79)
Copying	43 (96)	38 (95)	34 (92)	52 (98)
Interview money	21 (47)	10 (25)*	9 (24)*	3 (5.7)‡

*$P<.05$ vs programs matching in none of the study years.
†$P<.01$ vs programs matching in none of the study years.
‡$P<.001$ vs programs matching in none of the study years.

A positive relationship existed between the size of the program and the number of years matched. Breakdown of the data showed a significant difference ($P<.0002$) in mean number of available PL1 positions in the programs matching 3 of 3 years (mean, 15.6) when compared with the groups matching 0, 1, and 2 of the 3 years (means of 9.1, 11.2, and 10.4), respectively (Fig 2). Ability to match favored the larger training programs. The number of benefits offered by programs matching 0, 1, 2, or 3 of the 3 study years is given in the Table. Further illustration of the significant relationships between frequency of matching and benefits can be seen in Fig 3. As noted in the "Materials and Methods" section, programs matching 0 of 3 years were used as the reference group. Reanalysis of the data using those programs matching 3 of 3 years as the reference group was exactly the same, with two minor exceptions. The first is that no significant difference was noted in life insurance for the programs that matched 2 of 3 years; the second is that the conference funds were no longer significant for the group that matched 1 of 3 years.

In looking at the number of programs adding benefits during the 3-year period, a significant difference was found in those programs matching 0 of 3 or 1 of 3 years vs 3 of 3 years ($P<.05$). Sixty-four percent and 79% of programs matching 0 of 3 years and 1 of 3 years, respectively, added new benefits, as compared with 17% of programs matching 3 of 3 years. In addition to those benefits listed in the Table, book allowances, retreats, maternity and paternity leave, and free access to MEDLINE were the most frequently cited additional benefits. Interestingly, $4 haircuts and $2 movies were also listed as benefits.

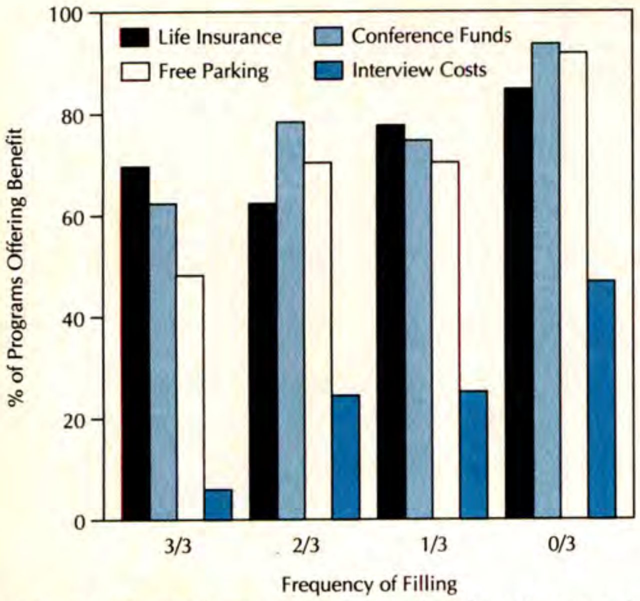

Fig 3.—*Percentage of programs offering various benefits vs matching 0, 1, 2, or 3 of 3 years, 1987 through 1989. See text for description of significant values.*

No significant differences were found in frequency of PL1 night call and the number of years matched. The mean frequency of call between the various groups ranged from every 3.37 to 3.55 nights for 1987, from 3.51 to 3.62 nights for 1988, and from 3.64 to 3.75 nights for 1989. The number of programs decreasing the frequency of the PL1 call between 1987 and 1989 ranged from 19% to 25%. No meaningful relationship between number of call-free elective months and ability to fill through the NRMP was detected. Forty-seven programs offered no call-free months, while 23, 26, and 22 programs offered 1, 2, and 3 call-free months, respectively. Ten programs had 6 call-free months, with the highest number cited being 11 call-free months in a 36-month period.

A positive relationship, however, was demonstrated between ability to match and whether a program offered shared residency positions. Only 23% of programs matching 0 of 3 years offered shared positions, in comparison with 43% of those matching 3 of 3 years ($P<.04$).

The percent male vs female residents was also analyzed in relation to whether a program matched 0, 1, 2, or 3 of the 3 study years. A significant difference in the percent male vs percent female residents was found between programs matching 0 of 3 years and those matching 1, 2, or 3 of the 3 years. The former group was composed of 53% males in comparison with the latter groups, in which the male representation accounted for 45%, 45%, and 44%, respectively.

COMMENT

In a recent commentary appearing in *Pediatrics,* James E. Strain, MD, executive director of the American Academy of Pediatrics, focuses on the career choices of medical students.[9] He brings to our attention the concerning figures generated by the NRMP regarding the increased number of available PL1 positions in the face of a decreasing number of US medical graduate residency applicants. This is reflected in the field of pediatrics by a widening of the gap created by the discrepancy between available PL1 positions and matched PL1 positions. The resulting creation of a "buyers market" has led to a competitive climate among pediatric training programs.

Fourteen percent of program directors responded affirmatively to accepting candidates outside the NRMP. It is possible that of the 4% who did not answer the question or the 18% not responding to the survey, additional program directors also reserve positions outside the NRMP. These data are in keeping with data from the American Board of Pediatrics, which show that many more residents take the In-Training Examination than there are PL1 positions available through the NRMP (Robert Brownlee, MD, oral communication, June 1989). The excess number taking the In-Training Examination cannot be completely accounted for by the additional residents in medicine-pediatrics programs, primary pediatric programs, or those programs that do not participate in the NRMP (ie, military). These data imply that programs are offering additional positions outside the NRMP.

Similar trends to those seen with the categorical pediatric training programs can be seen with the medicine-pediatrics and primary pediatrics programs. The percentage of available NRMP positions that actually filled was greatest for the years 1986 and 1987. In 1987, 81.1% of available medicine-pediatric positions filled as compared with 59.7% in 1990. Likewise, 95% of available primary pediatric positions filled in 1986 as compared with 80.5% in 1990.[2,10] Thus, increasing interest in other than categorical pediatric programs is not a factor in the declining interest in the categorical programs. In fact, there seems to be a widespread decline in interest for primary care specialties in general. During the first half of the last decade, there was an increasing number of positions available through the NRMP for both family practice and internal medicine. As with pediatrics, the percentage of positions being filled likewise increased until 1985-1986. The year 1987 heralded the beginning of a decline in the percent of matched positions, culminating in a 10% drop for both family practice and internal medicine during the last 5 years.[2] This compares with a 5% decline for pediatrics.[2] A decrease in the total number of senior medical students seeking training positions may account for a small portion of this decline. We also speculate that economics and life-style play important roles in the choice of a subspecialty career over a primary care career.

Our search for factors associated with an ability to match led us to the following profile. The larger the program is, the more likely it is to match. Although we did not collect data regarding type of program (ie, children's hospital vs university hospital vs community hospital), children's hospitals and university hospitals tend to have the larger programs. Programs matching all 3 years were more likely to offer shared residency positions. There seems to be a negative relationship between some of the benefits and ability to match. We interpret this to mean that programs that have a good track record for matching feel less compelled to offer such benefits as free parking, conference funds, interview money, and life insurance. Also, during the past 3 years the ability to match was associated with the addition of fewer benefits, again leading us to believe that the programs that have little or no difficulty matching do not feel pressured to improve their benefit package in contrast to those programs having greater difficulty filling their positions.

The PL1 call schedule had no influence on ability to match through the NRMP. This may be explained by the similarity among the four groups for mean frequency of PL1 nights on call. A meaningful relationship between the number of call-free elective months and ability to match could not be substantiated by our data. Most programs offer 0, 1, 2, or 3 call-free months despite a range of up to 11 call-free months.

The positive relationship between ability to match and the offering of shared residency positions may in some way be interrelated with program size and percentage of female residents, the latter two variables also being positively associated with ability to match. One may speculate that larger training programs have the flexibility to offer part-time or shared residency training positions and that this may be particularly appealing to women who have other family obligations.

The major problem with this descriptive study is that we may not have identified other variables that may have an influence on a program's ability to match. Geographic location may be a critical factor, but we did not evaluate this aspect. We thought that some program directors would be inhibited by our potential ability to trace the questionnaire to a specific program based on geographic location and size of the residency training program. The reputation of a program in the academic community may also bear a strong influence on ability to match, but there is no way to quantify this variable objectively.

In light of our findings, we contend that the focus of our efforts as pediatricians should not be to make our training programs more competitive in attracting fourth-year students interested in pediatrics but rather to influence the career choices of students early in medical school, thereby increasing the pool of medical students who enter pediatrics.

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WARNINGS: USE ONLY THE ALUMINUM HYDROXIDE DILUENT SUPPLIED. If PedvaxHIB is used in persons with malignancies or in those who are receiving immunosuppressive therapy or who are otherwise immunocompromised, the expected immune response may not be obtained.

PRECAUTIONS: ***General:*** As for any vaccine, adequate treatment provisions, including epinephrine, should be available for immediate use should an anaphylactoid reaction occur. As with other vaccines, PedvaxHIB may not induce protective antibody levels immediately following vaccination. As with any vaccine, vaccination with PedvaxHIB may not result in a protective antibody response in all individuals given the vaccine. As reported with Haemophilus b polysaccharide vaccine and another Haemophilus b conjugate vaccine, cases of Haemophilus b disease may occur in the week after vaccination, prior to the onset of the protective effects of the vaccines. There is insufficient evidence that PedvaxHIB given immediately after exposure to natural *Haemophilus influenzae* type b will prevent illness. Any acute infection or febrile illness is reason for delaying use of PedvaxHIB except when, in the opinion of the physician, withholding the vaccine entails a greater risk.

Laboratory Test Interactions: Sensitive tests (e.g., Latex Agglutination Kits) may detect PRP derived from the vaccine in urine of some vaccinees for up to seven days following vaccination with PedvaxHIB; in clinical studies with PedvaxHIB, such children demonstrated normal immune response to the vaccine.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: PedvaxHIB has not been evaluated for its carcinogenic or mutagenic potential or for its potential to impair fertility.

Pregnancy: *Pregnancy Category C:* Animal reproduction studies have not been conducted with PedvaxHIB. It is also not known whether PedvaxHIB can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. PedvaxHIB is not recommended for use in pregnant women.

ADVERSE REACTIONS: In early clinical studies involving the administration of 8,086 doses of PedvaxHIB alone to 5,027 healthy infants and children 2 months to 71 months of age, PedvaxHIB was generally well tolerated. No serious adverse reactions were reported. During a two-day period following vaccination with PedvaxHIB in a subset of these infants and children, the most frequently reported adverse reactions, excluding those shown in the first table, in decreasing order of frequency, included: irritability, sleepiness, respiratory infection/symptoms, and ear infection/otitis media. Urticaria was reported in two children. Thrombocytopenia was seen in one child. A cause-and-effect relationship between these side effects and the vaccination has not been established.

Selected objective observations reported by parents over a 48-hour period in infants and children 2 to 71 months of age following primary vaccination with PedvaxHIB alone are summarized in the first table.

In The Protective Efficacy Study, 4,459 healthy Navajo infants 6 to 12 weeks of age received PedvaxHIB or placebo. Most of these infants received DTP/OPV concomitantly. No differences were seen in the type and frequency of serious health problems expected in this Navajo population or in serious adverse experiences reported among those who received PedvaxHIB and those who received placebo, and none was reported to be related to PedvaxHIB. Only one serious reaction (tracheitis) was reported as possibly related to PedvaxHIB and only one (diarrhea) as possibly related to placebo. Seizures occurred infrequently in both groups (9 occurred in vaccine recipients, 8 of whom also received DTP; 8 occurred in placebo recipients, 7 of whom also received DTP) and were not reported to be related to PedvaxHIB. The frequencies of fever and local reactions occurring in a subset of these infants during a 48-hour period following each dose were similar to those seen in early clinical studies (see first table).

As with any vaccine, there is the possibility that broad use of PedvaxHIB could reveal adverse reactions not observed in clinical trials.

Potential Adverse Reactions: The use of Haemophilus b polysaccharide vaccines and another Haemophilus b conjugate vaccine has been associated with the following additional adverse effects: early onset of Haemophilus b disease and Guillain-Barré syndrome. A cause-and-effect relationship between these side effects and the vaccination was not established.

Fever or Local Reactions in Subjects 2 to 71 Months of Age Vaccinated with PedvaxHIB Alone: Other Clinical Studies

		Dose 1				Dose 2			
Age (Months)	Reaction	Number of Subjects Evaluated	6 hr.	24	48	Number of Subjects Evaluated	6 hr.	24	48
2-14*	Fever >38.3°C (101°F) Rectal	532	2.4%	3.8%	1.9%	329	3.0%	4.3%	3.6%
	Erythema >2.5 cm diameter	1,026	0.2%	1.0%	0.4%	585	0.9%	1.2%	0.7%
	Swelling/ Induration >2.5 cm diameter	1,026	0.6%	1.5%	1.6%	585	0.9%	2.8%	3.7%
15-71**	Fever >38.3°C (101°F) Rectal	149	4.0%	4.0%	6.7%				
	Erythema >2.5 cm diameter	572	0.0%	0.3%	0.2%				
	Swelling/ Induration >2.5 cm diameter	572	0.9%	2.1%	1.4%				

*Additional complaints reported following vaccination with the first and second dose of PedvaxHIB, respectively, in the indicated number of subjects were: nausea, vomiting, and/or diarrhea (101, 41), crying for more than one-half hour (43, 15), rash (16, 17), and unusual high-pitched crying (4, 4).

**Additional complaints reported following vaccination with one dose of PedvaxHIB in the indicated number of subjects were: nausea, vomiting, and/or diarrhea (44), crying for more than one-half hour (19), rash (12), and unusual high-pitched crying (0).

DOSAGE AND ADMINISTRATION:

FOR INTRAMUSCULAR ADMINISTRATION. DO NOT INJECT INTRAVENOUSLY.

2 to 14 Months of Age: Infants 2 to 14 months of age should receive a 0.5-mL dose of vaccine ideally beginning at 2 months of age followed by a 0.5-mL dose 2 months later (or as soon as possible thereafter). When the primary two-dose regimen is completed before 12 months of age, a booster dose is required (see text and second table).

15 Months of Age and Older: Children 15 months of age and older previously unvaccinated against Haemophilus b disease should receive a single 0.5-mL dose of vaccine.

Booster Dose: In infants completing the primary two-dose regimen before 12 months of age, a booster dose (0.5 mL) should be administered at 12 months of age but not earlier than 2 months after the second dose.

DATA ARE NOT AVAILABLE REGARDING THE INTERCHANGEABILITY OF OTHER HAEMOPHILUS b CONJUGATE VACCINES AND PedvaxHIB® (Haemophilus b Conjugate Vaccine [Meningococcal Protein Conjugate], MSD).

Vaccination Regimens by Age Group
(see text for details)

Age (Months) at First Dose	Primary	Age (Months) at Booster Dose
2-10	2 doses, 2 months apart	12
11-14	2 doses, 2 months apart	—
15-71	1 dose	—

TO RECONSTITUTE, USE ONLY THE ALUMINUM HYDROXIDE DILUENT SUPPLIED.

First, agitate the diluent vial; then, using sterile technique, withdraw the entire volume of aluminum hydroxide diluent into the syringe to be used for reconstitution. Inject all the aluminum hydroxide diluent in the syringe into the vial of lyophilized vaccine, and agitate to mix thoroughly.

Withdraw the entire contents into the syringe and inject the total volume of reconstituted vaccine (0.5 mL) intramuscularly, preferably into the anterolateral thigh or the outer aspect of the upper arm.

It is recommended that the vaccine be used as soon as possible after reconstitution. Store reconstituted vaccine in the vaccine vial at 2° to 8°C (36° to 46°F) and discard if not used within 24 hours. Agitate prior to injection.

Parenteral drug products should be inspected visually for extraneous particulate matter and discoloration prior to administration whenever solution and container permit. Aluminum hydroxide diluent and PedvaxHIB when reconstituted are slightly opaque white suspensions.

Special care should be taken to ensure that the injection does not enter a blood vessel.

It is important to use a separate sterile syringe and needle for each patient to prevent transmission of hepatitis B or other infectious agents from one person to another.

HOW SUPPLIED: No. 4792—PedvaxHIB is supplied as a single-dose vial of lyophilized vaccine, NDC 0006-4792-00, and a vial of aluminum hydroxide diluent.

No. 4797—PedvaxHIB is supplied as follows: a box of 5 single-dose vials of lyophilized vaccine, NDC 0006-4797-00, and 5 vials of aluminum hydroxide diluent.

Storage: Before reconstitution, store PedvaxHIB at 2° to 8°C (36° to 46°F). Store reconstituted vaccine in the vaccine vial at 2° to 8°C (36° to 46°F) and discard if not used within 24 hours.

DO NOT FREEZE the aluminum hydroxide diluent or the reconstituted vaccine.

For more detailed information, consult your MSD Representative or see Prescribing Information.

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JOVA08(802)

Commotio Cordis

The Single, Most Common Cause of Traumatic Death in Youth Baseball

Thomas J. Abrunzo, MD

• Two cases of blunt chest trauma caused by a baseball are reported, including one death. At least one of these was in consequence of cardiac concussion or commotio cordis, an entity not described in the pediatric literature. Concussion of the heart is a functional injury, in contrast to cardiac contusion or cardiac rupture, which pertains to structural injury. However, a cardiac concussion appears more likely to have immediate, dire consequences than the structural injury of cardiac contusion. Both of the cases presented occurred in the Little League baseball setting. Blunt chest trauma is reported to cause two to three deaths in youth baseball each year. There appears to be an increased pediatric susceptibility to this type of injury. Unfortunately, these cases are quite resistant to resuscitative therapy. Devices and techniques for primary and secondary prevention exist, but have yet to be systematically verified and implemented.

(*AJDC.* 1991;145:1279-1282)

Clinically significant chest trauma in children is usually described in the setting of a major force, such as an automobile accident or fall from an extreme height.[1,2] There has been little recognition that youth sports present yet another route for fatal blunt cardiac injury, and even less recognition that these fatalities can occur in the absence of structural injury to the heart. The spectrum of blunt cardiac injury extends from a concussion ("a violent jar or shock")[3] to gross, structural disruption.[4,5] Unfortunately, a concussion can cause mortal injury as quickly as a ruptured ventricle. Published data regarding commotio cordis (CC) reveal current resuscitation attempts as uniformly unsuccessful. Successful resuscitation may involve the use of the precordial thump, a technique not generally recommended for children. Difficulties in resuscitating patients with this problem dramatize the importance of primary and secondary prevention, that is, avoiding exposure and early treatment, respectively. Two illustrative cases are presented.

PATIENT REPORTS

PATIENT 1.—The patient, a healthy 10-year-old boy, was a right-handed batter in the Little League for 9- to 12-year-old children. The pitcher was 9 years old and not remarkable for his pitching velocity, according to bystanders. There was informal, unsubstantiated consensus that he was throwing "about 30 mph." A pitch struck the batter in the left side of the chest and he was momentarily stunned. He fell to the ground and witnesses reported gasping respirations. A bystander found the carotid pulse to be present. However, the victim was almost immediately pale and cyanotic. Within about 30 seconds, the pulse was not felt and two-person cardiopulmonary resuscitation was begun by a nurse and paramedic bystander. Emergency medical services paramedics arrived at the scene within 8 minutes of the event. The victim was apneic, cyanotic, and the electrocardiogram was interpreted as fine ventricular fibrillation. His pupils were fixed and dilated. Serial defibrillations of 100 J, 100 J, and 200 J produced no change in rhythm. The boy's trachea was intubated and 0.5 mg of epinephrine was administered endotracheally. The rhythm continued in either fine ventricular fibrillation or asystole. The boy was transported by helicopter to our pediatric emergency department, receiving assisted ventilations and external cardiac compressions. On arrival in the emergency department, endotracheal tube placement was confirmed by auscultation and chest roentgenography. Cardiac rhythm was noted to be asystole. On physical examination, an approximately 3- to 4-cm crescentic ecchymosis just inferior and lateral to the left nipple was detected. As the patient was being evaluated, weight-estimated doses of

Department Editors.—*William B. Strong, MD, Augusta, Ga; Carl L. Stanitski, MD, Pittsburgh, Pa; Ronald E. Smith, PhD, Seattle, Wash; Jack H. Wilmore, PhD, Austin, Tex*

Purpose.—*This section provides current information related to the medical needs of young athletes, as pertinent to counseling young athletes and their parents regarding sports participation and practices contributing to the health maintenance of the athlete, as well as current concepts in the prevention, diagnosis, and treatment of sports-related illnesses and injuries.*

Editorial Comment.—*Commotio cordis, a rarely described entity in the pediatric literature, is a distinct entity of which the pediatrician should be aware. The trauma may be lethal, but fortunately is rare. Because of its rarity, there should be no community outcry for increasing protective garb, eg, chest protectors, for youth baseball players. Life is a risk! We, unfortunately, do not live in a risk-free society. To attempt to make youth sports absolutely risk-free would be so expensive that no children or few children would benefit from the wonders of sports participation.*—W.B.S.

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From Pediatric Emergency Services, St Joseph's Hospital, Tampa, Fla.

Reprint requests to 2706 Fountain Blvd, Tampa, FL 33609 (Dr Abrunzo).

bicarbonate, epinephrine, atropine, and calcium were given; the dosages were repeated 5 minutes later. A continuous epinephrine infusion was ordered. A slow, wide-complex rhythm was generated. Pulse and blood pressure were absent. The pupils remained fixed and dilated. The patient was pronounced dead when no further cardiovascular or neurologic response to therapy was elicited. Autopsy revealed the heart to be free of gross or microscopic evidence of injury or congenital abnormality.

PATIENT 2.—An 11-year-old male baseball player was struck in the mid and upper sternum by a Little League regulation baseball thrown by another player during practice. The ball was "pegged hard" according to the victim's later recollection. Two adult witnesses reported the victim's immediate collapse. The boy fell forward, landing prone on the grass. Within 15 seconds, witnesses turned the patient supine, noting that his eyes were rolled back and his mouth was clenched, and that he did not respond to verbal and tactile stimuli. Urinary incontinence was evident. Cyanosis was not noted. His pulse rate was not evaluated. Witnesses attempted unsuccessfully to open the boy's clenched mouth. About 30 to 60 seconds into the event, attempts at cardiopulmonary resuscitation by chest compression were begun. After an estimated 10 compressions, the boy roused and became verbally responsive. He was found alert and responsive by emergency medical services personnel who arrived at the scene within 10 minutes of onset of the event. The boy arrived at our facility with normal, stable vital signs and normal mental status. Physical examination showed no external signs of chest trauma. The patient pointed to the mid and upper sternum as the site of chest impact, but denied pain or tenderness. No swelling, erythema, or ecchymosis was noted. Results of a cardiac examination, including inspection of the precordium, auscultatory evaluation of the first and second heart sounds, precordial and distal pulse palpation, jugular venous pulse, liver palpation, and examination for peripheral edema, were all negative. Electrocardiographic monitoring, venous access, and blood sampling for a complete blood cell count, electrolytes, and fractionated creatine kinase were ordered. The initial electrocardiogram showed minimal ST segment elevation, which was not present on an electrocardiogram done 24 hours later. The initial creatine kinase level was elevated to 396 U/L (normal range for age, 30 to 230 U/L). The initial creatine kinase–MB fraction level was 3.6 ng/mL, and at 24 hours after injury, 3.5 ng/mL (normal range, 0 to 7 ng/mL). An echocardiogram was reported as normal. The patient's medical history was significant for hospitalization at 5 years of age for episodes of "falling asleep in school." This evaluation, including electroencephalogram and Holter monitoring, revealed no abnormalities and the episodes did not recur. There was no family history of congenital heart disease, seizures, or premature death. The patient played youth football, basketball, and baseball without ever experiencing exertional syncope or near-syncope. He was discharged after an uneventful 3 days of observation. He was to be reevaluated in 2 weeks.

COMMENT

The US Consumer Product Safety Commission has generated data implicating ball impact to the chest as the single, most common cause of traumatic death in youth baseball.[6,7] However, these data appear not to have affected the community's main child health advocates—pediatricians.

Blunt cardiac injury in children has received little attention in the pediatric literature. Cardiac concussion is not even mentioned in standard texts in pediatrics,[8,9] pediatric cardiology,[10,11] pediatric surgery,[12] pediatric trauma,[13,14] pediatric intensive care,[15] or pediatric emergency medicine.[16]

The spectrum of blunt cardiac injury includes gross disruption of the anatomy, such as rupture of the ventricles, ventricular septum, chordae tendineae, or the cardiac valves; less severe damage causing contusion of myocardium, often involving elevation of serum cardia enzymes and various electrocardiogram changes; an concussion or functional, nonstructural injury causin dysrhythmia.[4,5] This latter injury, known as CC, probabl exists in a transient, benign form. Such cases are probably not generally recognized or subjected to medica analysis. Patient 2 appears to represent an incrementa level of involvement, with objective, but self-limited sign and symptoms. Patient 1 represents an extreme manifestation of CC, a malignant, irreversible form resulting i death. The incidence of CC in the population is no known.

The pediatric patient is generally thought to be more susceptible to thoracic parenchymal injury after nonpenetrating trauma than the adult. Thoracic organs can be damaged in the absence of obvious injury to the skin or ribs. This is generally attributed to a thinner layer of soft tissue in the chest wall, and increased compliance of the immature rib cage.[17] These latter factors enhance direct transmission of force to the underlying parenchyma. In addition, neuromuscular immaturity with respect to injury avoidance makes the child more liable to injury in general.[18]

Seven recent case reports of fatal CC from sports projectiles such as a baseball, softball, hockey puck, and lacrosse ball were found in the medical literature.[19-24] All the reports describe collapse within seconds, unsuccessful resuscitation, and postmortem findings negative for structural cardiac damage. They involve both children and young adults. The baseball and softball cases do not appear to involve great force.

The resistance of dysrhythmias in CC to resuscitative efforts is puzzling. In many of the cases reported, resuscitation was unsuccessful even when begun immediately after the injury was sustained. Liedtke et al[25] suggested temporary alterations in coronary blood flow as a possible explanation for the cardiopathy of CC.

Experimental cardiac trauma studies suggest that relatively low levels of blunt injury induced only dysrhythmias; intermediate energy levels produced varying degrees of contusion associated with impairment of ventricular function; and the highest levels of energy were nearly always fatal, causing gross, structural cardiac disruption.[26] It seems that dysrhythmia is a specific manifestation of CC, not the response of an abnormal host to trivial chest injury. Lindsey et al,[27] drawing on the work of German and Russian investigators, compared the differential features of cardiac concussion and contusion (Table).

Of particular interest in the Table is the characteristic immediate onset, loss of consciousness, hypotension, and immediate disturbance of rhythm and conduction that marks CC as distinct from, and more dangerous than, cardiac contusion.

Therapy for the child who collapses after blunt chest trauma seems to be the same as for any other emergency: airway maintenance, assisted ventilations, chest compressions, and defibrillation, as indicated by electrocardiographic monitoring.[28] The lack of efficacy in the cases reviewed is disturbing. One might speculate on the possible use of the precordial thump. This maneuver is used for the adult victim of witnessed ventricular fibrillation.[29] Indeed, if ventricular fibrillation is the mechanism of death in CC, it seems reasonable to employ the precordial thump; if unsuccessful, immediate cardiopulmonary resuscitation should be instituted. In the past, the American Heart Association cautioned against the use of the pre-

Differential Features of Cardiac Concussion and Contusion

Feature	Concussion	Contusion
Site of trauma	Precordial only	Chest, anywhere
Direction of force	Sternum to vertebra	Insignificant
Force	Sharp, not necessarily violent	Generally violent
Thoracic cage intact	Essential	Not essential
Onset	Immediate	Gradual
Course	Transitory	Lasting
Loss of consciousness	As a rule	Not characteristic
Blood pressure	Frequently drops	Normal; rarely up
Disturbances of rhythm and conduction	Characteristic, immediate	Absent or delayed
Changes in ST segment and T waves	Generally absent	Always present

cordial thump in children.[30] This is because of the infrequency of ventricular fibrillation as a presenting arrhythmia, the possibility of iatrogenic trauma to the heart, and the propensity for converting a benign rhythm to a malignant one. A different approach to children is not addressed in the most recent publication of advanced cardiac life support standards.[29] The precordial thump should be scientifically evaluated for its potential as emergency therapy for pediatric CC.

Trauma has long been recognized as the "Number 1 killer of children."[31] Sports-related death from injury is much less commonly observed.[32,33] While the pediatric medical literature generally acknowledges the nontraumatic cardiac causes of youth sports deaths,[34-38] traumatic cardiac death has not generated much interest. This is notwithstanding information from the US Consumer Product Safety Commission stating that in the 10-year period from 1973 to 1983, 51 children from age 5 to 14 years died of baseball-related injury, 23 of whom died of ball impact to the chest.[6] This would make ball impact to the chest the single, most common cause of traumatic death in youth baseball. Deaths are reported within and outside the formal Little League setting, suggesting that adult supervision is not always protective. If helmets and genital cups are a standard part of Little League equipment, the incidence and lethality of blunt chest trauma should also mandate consideration of protective equipment. Manufacturers have already marketed a "reduced injury factor" ball of lower mass and momentum than the standard ball (*Tampa Tribune*. March 29, 1990:1-C). Protective vests are also currently marketed (*Tampa Tribune*. April 26, 1990:3-B). The data available demand that more information be gathered and that protective devices be evaluated with the purpose of their implementation in youth baseball.[39,40]

SUMMARY

Commotio cordis or concussion of the heart is a distinct entity from cardiac contusion. It has received little attention as a source of pediatric mortality. It appears to be the single, most common cause of traumatic death in youth baseball. Although infrequent, its apparent resistance to therapy, high lethality, and prevalence in youth baseball indicate the aggressive implementation of prevention efforts.

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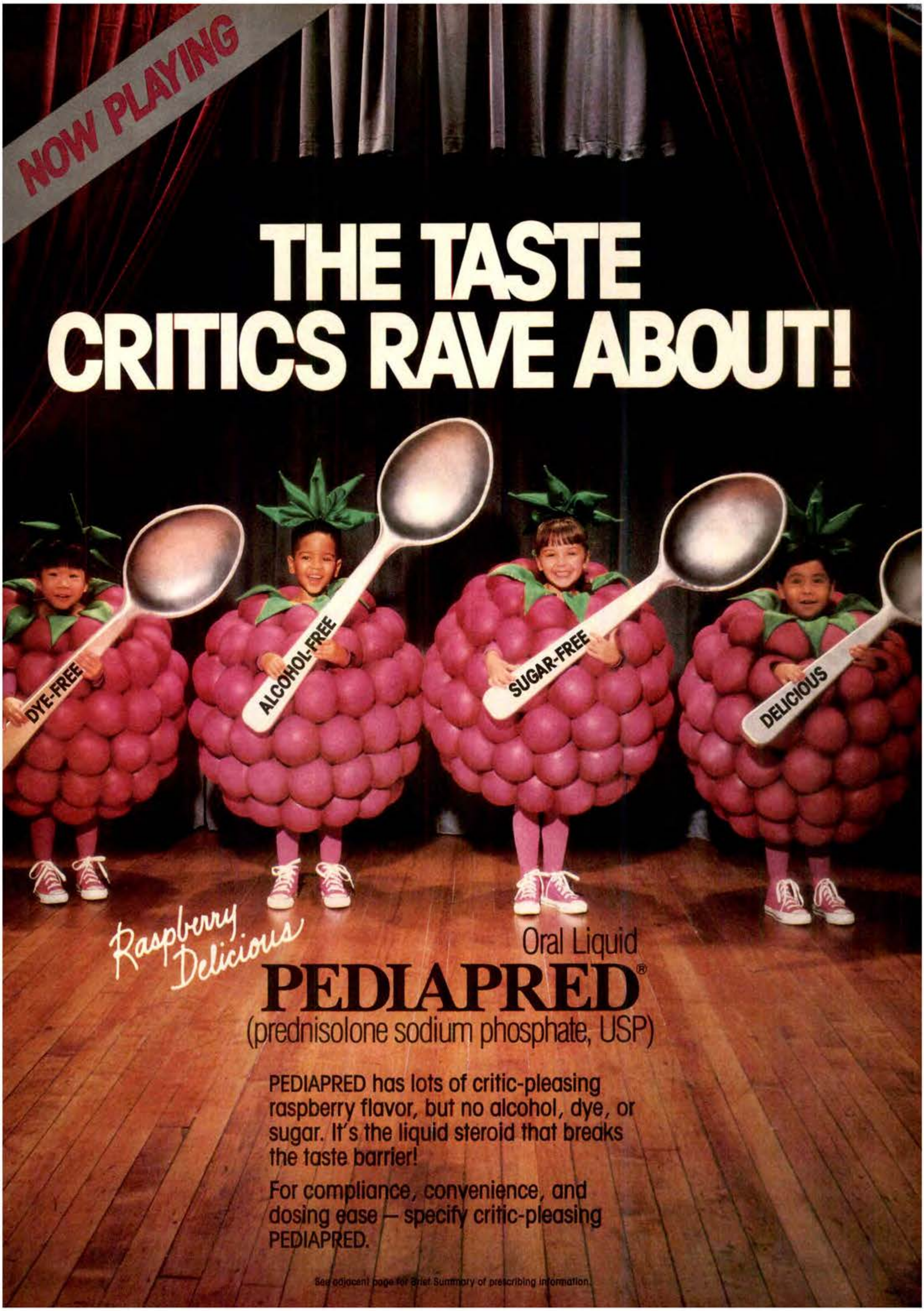
Trauma During Pregnancy: A Review of 79 Cases

Thomas J. Esposito, MD, MPH; David R. Gens, MD;
Lynn Gerber Smith, RN, MS; Ronald Scorpio, MD;
Timothy Buchman, MD (*Arch Surg.* 1991;126:1073-1078)

Trauma in Pregnancy: Predicting Pregnancy Outcome

David P. Kissinger, MD; Grace S. Rozycki, MD;
John A Morris, Jr, MD; M. Margaret Knudson, MD;
Wayne S. Copes, PhD; Sue M. Bass, ScM; H. Kendle Yates;
Howard R. Champion, FRCS(Edin)
(*Arch Surg.* 1991;126:1079-1086)



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12. **Nervous System**–Acute exacerbations of multiple sclerosis
13. **Miscellaneous**–Tuberculous meningitis with subarachnoid block or impending block when used concurrently with appropriate antituberculous chemotherapy; trichinosis with neurologic or myocardial involvement

CONTRAINDICATIONS: Systemic fungal infections.

WARNINGS: In patients on corticosteroid therapy subjected to unusual stress, increased dosage of rapidly acting corticosteroids before, during and after the stressful situation is indicated.

Corticosteroids may mask some signs of infection, and new infections may appear during their use. There may be decreased resistance and inability to localize infection when corticosteroids are used.

Prolonged use of corticosteroids may produce posterior subcapsular cataracts, glaucoma with possible damage to the optic nerves, and may enhance the establishment of secondary ocular infections due to fungi or viruses.

Average and large doses of hydrocortisone or cortisone can cause elevation of blood pressure, salt and water retention, and increased excretion of potassium. These effects are less likely to occur with the synthetic derivatives except when used in large doses. Dietary salt restriction and potassium supplementation may be necessary. All corticosteroids increase calcium excretion. **While on corticosteroid therapy patients should not be vaccinated against smallpox. Other immunization procedures should not be undertaken in patients who are on corticosteroids, especially on high doses, because of possible hazards of neurological complications and a lack of antibody response.**

The use of prednisolone in active tuberculosis should be restricted to those cases of fulminating or disseminated tuberculosis in which the corticosteroid is used for the management of the disease in conjunction with an appropriate antituberculous regimen.

If corticosteroids are indicated in patients with latent tuberculosis or tuberculin reactivity, close observation is necessary as reactivation of the disease may occur. During prolonged corticosteroid therapy these patients should receive chemoprophylaxis.

PRECAUTIONS: General: Drug-induced secondary adrenocortical insufficiency may be minimized by gradual reduction of dosage. This type of relative insufficiency may persist for months after discontinuation of therapy; therefore, in any situation of stress occurring during that period, hormone therapy should be reinstituted. Since mineralocorticoid secretion may be impaired, salt and/or a mineralocorticoid should be administered concurrently.

There is an enhanced effect of corticosteroids in patients with hypothyroidism and in those with cirrhosis.

Corticosteroids should be used cautiously in patients with ocular herpes simplex because of possible corneal perforation.

The lowest possible dose of corticosteroid should be used to control the condition under treatment, and when reduction in dosage is possible, the reduction should be gradual.

Psychic derangements may appear when corticosteroids are used, ranging from euphoria, insomnia, mood swings, personality changes, and severe depression, to frank psychotic manifestations. Also, existing emotional instability or psychotic tendencies may be aggravated by corticosteroids.

Aspirin should be used cautiously in conjunction with corticosteroids in hypoprothrombinemia.

Steroids should be used with caution in nonspecific ulcerative colitis, if there is a probability of impending perforation, abscess or other pyogenic infection; diverticulitis; fresh intestinal anastomoses; active or latent peptic ulcer; renal insufficiency; hypertension; osteoporosis; and myasthenia gravis.

Growth and development of infants and children on prolonged corticosteroid therapy should be carefully observed.

Although controlled clinical trials have shown corticosteroids to be effective in speeding the resolution of acute exacerbations of multiple sclerosis, they do not show that they affect the ultimate outcome or natural history of the disease. The studies do show that relatively high doses of corticosteroids are necessary to demonstrate a significant effect. (See DOSAGE AND ADMINISTRATION.)

Since complications of treatment with glucocorticoids are dependent on the size of the dose and the duration of treatment, a risk/benefit decision must be made in each individual case as to dose and duration of treatment and as to whether daily or intermittent therapy should be used.

Information for Patients: Patients should be warned not to discontinue the use of PEDIAPRED abruptly or without medical supervision, to advise any medical attendants that they are taking PEDIAPRED and to seek medical advice at once should they develop fever or other signs of infection.

Drug Interactions: Drugs such as barbiturates which induce hepatic microsomal drug metabolizing enzyme activity may enhance metabolism of prednisolone and require that the dosage of PEDIAPRED be increased.

Pregnancy: Pregnancy Category C - Prednisolone has been shown to be teratogenic in many species when given in doses equivalent to the human dose. There are no adequate and well controlled studies in pregnant women. PEDIAPRED should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Animal studies in which prednisolone has been given to pregnant mice, rats and rabbits have yielded an increased incidence of cleft palate in the offspring.

Nursing Mothers: Prednisolone is excreted in breast milk, but only to a small (less than 1% of the administered dose) and probably clinically insignificant extent. Caution should be exercised when PEDIAPRED is administered to a nursing woman.

ADVERSE REACTIONS:

Fluid and Electrolyte Disturbances
Sodium retention; fluid retention; congestive heart failure in susceptible patients; potassium loss; hypokalemic alkalosis; hypertension

Musculoskeletal
Muscle weakness; steroid myopathy; loss of muscle mass; osteoporosis; vertebral compression fractures; aseptic necrosis of femoral and humeral heads; pathologic fracture of long bones

Gastrointestinal
Peptic ulcer with possible perforation and hemorrhage; pancreatitis; abdominal distention; ulcerative esophagitis

Dermatologic
Impaired wound healing; thin fragile skin; petechiae and ecchymoses; facial erythema; increased sweating; may suppress reactions to skin tests

Metabolic
Negative nitrogen balance due to protein catabolism

Neurological
Convulsions; increased intracranial pressure with papilledema (pseudotumor cerebri) usually after treatment; vertigo; headache

Endocrine
Menstrual irregularities; development of cushingoid state; secondary adrenocortical and pituitary unresponsiveness, particularly in times of stress, as in trauma, surgery or illness; suppression of growth in children; decreased carbohydrate tolerance; manifestations of latent diabetes mellitus; increased requirements for insulin or oral hypoglycemic agents in diabetes

Ophthalmic
Posterior subcapsular cataracts; increased intraocular pressure; glaucoma; exophthalmos

OVERDOSAGE: The effects of accidental ingestion of large quantities of prednisolone over a very short period of time have not been reported, but prolonged use of the drug can produce mental symptoms, moon face, abnormal fat deposits, fluid retention, excessive appetite, weight gain, hypertrichosis, acne, striae, ecchymosis, increased sweating, pigmentation, dry scaly skin, thinning scalp hair, increased blood pressure, tachycardia, thrombophlebitis, decreased resistance to infection, negative nitrogen balance with delayed bone and wound healing, headache, weakness, menstrual disorders, accentuated menopausal symptoms, neuropathy, fractures, osteoporosis, peptic ulcer, decreased glucose tolerance, hypokalemia, and adrenal insufficiency. Hepatomegaly and abdominal distention have been observed in children.

Treatment of acute overdosage is by immediate gastric lavage or emesis. For chronic overdosage in the face of severe disease requiring continuous steroid therapy the dosage of prednisolone may be reduced only temporarily, or alternate day treatment may be introduced.

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Acellular Pertussis Vaccines

Efficacy and Evaluation of Clinical Case Definitions

William C. Blackwelder, PhD; Jann Storsaeter, MD; Patrick Olin, MD, PhD; Hans O. Hallander, MD, PhD

• The efficacy of two acellular pertussis vaccines was estimated for various clinical case definitions, with and without the requirement of culture confirmation, from a randomized trial in Sweden. Efficacy increased with duration of coughing spasms and when the case definition included whoops or whoops plus at least nine coughing spasms a day. After deletion of clinical cases not believed to be caused by pertussis, efficacies were closer to the higher values for culture-confirmed disease. Nonspecificity of the clinical criterion "21 days of coughing spasms with whoops" resulted in estimates of predictive value for pertussis of 85% for placebo recipients and 56% for vaccinees. We conclude that laboratory confirmation of suspected cases is needed in pertussis vaccine trials. A suggested case definition is 21 days or more of coughing spasms with confirmation by culture, serologic study, or household exposure to culture-confirmed pertussis.

(*AJDC.* 1991;145:1285-1289)

Reduced pertussis disease incidence in the Japanese population after the introduction of acellular pertussis vaccines in 1981 has been reported.[1] A randomized, double-blind, placebo-controlled trial of two acellular pertussis vaccines was conducted in Sweden during 1986 to 1987.[2] Estimated efficacy against any culture-confirmed pertussis disease was 54% (95% confidence interval, 26% to 72%) for a single-component vaccine and 69% (95% confidence interval, 47% to 82%) for a two-component vaccine; efficacy against culture-confirmed disease with a cough lasting more than 30 days was 80% and 79%, respectively. Unblinded posttrial passive surveillance yielded somewhat higher efficacy estimates. These higher estimates may be due to observer bias; on the other hand, the active surveillance during the double-blind trial may have detected milder cases that would have gone unrecognized under routine circumstances.[3]

No acellular pertussis vaccine has yet been licensed outside Japan, and further randomized trials of acellular vaccines are being planned. Some of these trials will compare acellular and whole-cell vaccines directly. The trials will be costly, requiring thousands of infants and several years to complete. Crucial to their success will be the case definition(s) used to determine the risk of pertussis disease.

We performed the present analysis (1) to assess the efficacy of the vaccines in the Swedish trial against clinical disease, using a variety of clinical case definitions; (2) to compare the estimates with those obtained when culture confirmation is also required; and (3) to explore the suitability for a future trial of a case definition based solely on clinical criteria.

SUBJECTS AND METHODS

The trial was approved by ethics committees at the Karolinska Institute, Stockholm, Sweden, and at Umeå, Uppsala, and Linköping universities, also in Sweden. Human subjects' clearances were obtained from the World Health Organization, Geneva, Switzerland, and the National Institute of Allergy and Infectious Diseases, Bethesda, Md. Oral informed consent was obtained from parents.

Clinical Methods

The methods of the trial have been described elsewhere.[2,4] The two acellular pertussis vaccines tested were developed at the National Institute of Health (JNIH) (Tokyo, Japan). Because there has been no routine immunization of infants against pertussis in Sweden since 1979, inclusion of a placebo group was considered ethical. Hence, infants aged 6 months to 1 year were randomized to receive two deep subcutaneous injections of a single-component (JNIH-7) or a two-component (JNIH-6) vaccine or placebo. The dose of each injection was 0.5 mL. The JNIH-7 vaccine contained 12 μg of protein nitrogen per milliliter of pertussis toxin (PT), and the JNIH-6 vaccine contained 7.5 μg per milliliter of PT and an equal amount of filamentous hemagglutinin (FHA). The first injection was given between February and April 1986, and the second injection was scheduled for 8 to 12 weeks later. After the second injection, study children were followed up in an active surveillance system either until the end of the study (August 1987) or until they had culture-confirmed pertussis disease. During follow-up, parents were told to call a study nurse if the study child coughed for more than 7 days, if whooping cough was diagnosed or suspected in any household member, or if any of certain specific symptoms (eg, whoops, coughing spasms, or cough with vomiting) occurred in any household member. Coughing spasms (paroxysmal cough) were

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From the National Institute of Allergy and Infectious Diseases, Bethesda, Md (Dr Blackwelder), and the Department of Pediatrics, Karolinska Institute, Sachs' Children's Hospital (Drs Storsaeter and Olin), and the National Bacteriological Laboratory (Dr Hallander), Stockholm, Sweden.

Reprint requests to BHV, Drakenbergsgatan 39, S-117 41 Stockholm, Sweden (Dr Storsaeter).

defined as "sudden periodic attacks of coughing." A whoop was defined as a "sonorous and convulsive inspiratory sound following paroxysmal cough."

Study nurses were instructed to interview parents each month by telephone about possible pertussis in the household. When pertussis was suspected in a study child, clinical information and nasopharyngeal swabs were collected by a study nurse; swabs were collected again 1 week later if the child was still coughing and the first culture had been negative. In addition, in most cases, blood samples were obtained within 14 days after the onset of cough ("acute" specimen) and at least 6 weeks after the onset of cough ("convalescent" specimen). The household was monitored until the last day of coughing.

Randomization

Study participants were randomized into groups of eight within each of 13 study sites in a ratio of placebo to JNIH-6 vaccine to JNIH-7 vaccine of 2:3:3. It has been demonstrated that the randomization resulted in very similar distributions for various characteristics of study children and their families.[2]

Estimation of Risk and Efficacy

Risk of pertussis during 15 months of follow-up, beginning 30 days after the second injection of vaccine or placebo, was estimated for various case definitions with the use of the actuarial method.[5] This method involves division of the period of follow-up into smaller intervals (in our case, 30-day intervals) and calculation of overall risk from estimates for each interval, which account for unavailability for follow-up. Some children had more than one recorded episode. All recorded episodes were used in this analysis, but a child was counted as a case only once for any particular case definition. Vaccine efficacy was estimated by the usual formula: $1 - p_v/p_u$, where p_v and p_u are estimated risks in vaccinated and unvaccinated children, respectively. Two-sided 95% confidence intervals for vaccine efficacy were obtained with use of a normal approximation for the natural logarithm of an observed proportion[6] and SEs were obtained from the actuarial analysis.

We calculated vaccine efficacy for clinical case definitions based on some combination of the following criteria: duration of coughing spasms (at least 1, 14, 21, 28, or 35 days), whoops, and nine or more coughing spasms on at least 1 day. The criterion for number of coughing spasms a day has been used previously as an indicator of moderate or severe disease.[7] Efficacy was also calculated when culture confirmation was required as part of the definition. In addition, we calculated efficacy against 21 days or more of coughing spasms with whoops after adjustment for nonpertussis disease, ie, cases that satisfied the clinical definition but could not be verified as being caused by pertussis infection by culture, serologic studies, or information concerning exposure.

An illness was considered a "nonpertussis case" if the culture was negative, if serologic data were available but no criterion for pertussis was met, and if there was no documented exposure to pertussis infection. Any of the following serologic criteria were considered verification of pertussis disease: a titer rise from acute to convalescent serum of at least two dilution steps by Chinese hamster ovary cell assay, which is specific for PT[8]; a 50% or greater increase in IgG antibody to PT or FHA as determined by enzyme-linked immunosorbent assay; or a 100% or greater increase in IgA antibody to PT or FHA as determined by enzyme-linked immunosorbent assay. The combination of these criteria was previously found to be nearly 100% sensitive in the detection of culture-positive pertussis disease.[4]

The proportion of nonpertussis cases was estimated by dividing the number of unverified cases by the number for which culture and serologic information was available. Estimation was performed separately for each study group (placebo, JNIH-7 vaccine, and JNIH-6 vaccine groups) and also for all vaccinees combined. The predictive value of the clinical case definition, or probability of pertussis given clinical disease, is a function of both the true attack rate and the probability of a false-positive result (ie, $1 - \text{specificity}$).[9] If specificity is uniform in the study population but the attack rate is lower in vaccinees than in placebo recipients, then the predictive value will also be lower for vaccinees. Predictive value was estimated by subtracting the proportion of nonpertussis cases from 1. The estimate of predictive value was then multiplied by the actuarial estimate of risk, with the use of predictive value for all vaccinees combined in the adjustment for JNIH-7 and JNIH-6 vaccine recipients. The adjusted risks were used to obtain an adjusted estimate of efficacy.

Statistical Tests

Risk estimates and proportions of unverified cases were compared with the χ^2 test with continuity correction.[10] All P values reported correspond to two-tailed tests; $P<.05$ was considered statistically significant. No correction was made for multiple comparisons; hence, we would expect approximately 5% of the tests to be significant by chance alone.

RESULTS

Of 3801 infants who received the first trial injection, 3711 received two injections and were available for follow-up for pertussis beginning 30 days after the second injection: 923 received placebo, 1403 received the JNIH-7 vaccine, and 1385 received the JNIH-6 vaccine. Exactly one episode with coughing spasms was reported for 764 children, two episodes for 141 children, three episodes for 13 children, and four episodes for three children ($n = 921$). Episodes with 21 days or more of spasms were reported for 319 children; the numbers of children with one, two, three, and four episodes were 299, 16, 3, and 1, respectively.

Table 1 gives risk estimates according to various clinical case definitions, with and without the requirement of culture confirmation, as well as point and interval estimates for vaccine efficacy. For both vaccines, but particularly the JNIH-7 vaccine, efficacy against coughing spasms of any duration was very low. Efficacy increased sharply for longer durations of coughing spasms. When whoops were added to the case definition, point estimates of efficacy increased, especially for the JNIH-7 vaccine. The addition of nine or more spasms on at least 1 day to the definition resulted in even higher efficacy estimates (data not shown).

Efficacy against clinical disease with 28 days or more of spasms and whoops was higher for the JNIH-7 than for the JNIH-6 vaccine (Table 1); the difference was statistically significant, both for all clinical disease and for culture-confirmed disease. However, no significant differences in efficacy were noted when whoops were not required in a case definition.

For illness with 21 days or more of coughing spasms, point estimates of efficacy were 27% for the JNIH-7 and 41% for the JNIH-6 vaccine (Table 1); the corresponding estimates for culture-confirmed disease were 75% and 81%, respectively. Similarly, for all other clinical case definitions as well, efficacy against culture-confirmed disease was higher than efficacy against any clinical disease, especially for illnesses with shorter durations of coughing spasms.

Among cases with 21 days or more of coughing spasms and whoops, the percentage that were not verified as pertussis by culture, serologic study, or exposure information was higher for JNIH-7 than JNIH-6 vaccine recipients, but the difference was not statistically significant

Table 1.—Estimates of Risk and Vaccine Efficacy

	Placebo (n=923)		JNIH-7 Vaccine (n=1403)				JNIH-6 Vaccine (n=1385)			
Case Definition	**No. of Cases**	**Risk, %†**	**No. of Cases**	**Risk, %†**	**VE, %‡**	**95% CI§**	**No. of Cases**	**Risk, %†**	**VE, %‡**	**95% CI§**
				All Cases Meeting Clinical Criteria						
1	249	27.5	359	26.2	5	(−10, 17)	313	23.0	16	(3, 27)
14	151	16.7	213	15.5	7	(−13, 23)	176	13.0	22	(5, 36)
21	107	11.8	118	8.7	27	(6, 43)	94	7.0	41	(23, 55)
28	73	8.1	60	4.4	46	(24, 61)	65	4.8	41	(18, 57)
1W	70	7.8	52	3.8	51	(30, 65)	64	4.7	39	(16, 56)
14W	57	6.4	33	2.5	62	(41, 75)	40	3.0	53	(31, 69)
21W	46	5.1	26	1.9	62	(39, 76)	27	2.0	60	(37, 75)
28W	35	3.9	8	0.6	85	(68, 93)	22	1.6	58	(29, 75)
				Culture-Confirmed Cases Only						
1	39	4.3	23	1.7	60	(33, 76)	14	1.1	75	(54, 86)
14	37	4.1	15	1.2	72	(48, 84)	11	0.9	79	(59, 89)
21	35	3.9	12	1.0	75	(53, 87)	10	0.8	81	(61, 90)
28	31	3.5	6	0.5	86	(66, 94)	10	0.8	78	(56, 89)
1W	33	3.7	5	0.4	89	(72, 96)	7	0.5	85	(67, 94)
14W	32	3.6	4	0.3	91	(74, 97)	7	0.5	85	(66, 93)
21W	30	3.4	4	0.3	90	(73, 97)	7	0.5	84	(63, 93)
28W	26	2.9	0	0.0	100	. . .	7	0.5	82	(57, 92)

*1, 14, 21, and 28 indicate days of coughing spasms; W indicates whoops on at least 1 day.
†Risk of pertussis with the indicated case definition, estimated by the actuarial method.
‡VE indicates vaccine efficacy (point estimate).
§95% CI indicates 95% confidence interval for vaccine efficacy.

(*P*>.20). However, the percentage not verified was significantly higher among all vaccinees combined than among placebo recipients (*P*<.01). Predictive value was estimated as 85% for placebo recipients and 56% for vaccinees. The adjusted pertussis risk estimates for placebo, JNIH-7 vaccine, and JNIH-6 vaccine recipients were 4.4%, 1.1%, and 1.1%, respectively. The estimated risk of nonpertussis disease with 21 days or more of coughing spasms and whoops (ie, probability of a false-positive result) was similar for vaccinees (0.8%) and placebo recipients (0.7%). After adjustment for clinical cases not considered to be caused by pertussis, point estimates for vaccine efficacy were much closer to those for culture-confirmed disease. The adjusted estimates for 21 and 28 days of coughing spasms with whoops were 75% and 91%, respectively, for the JNIH-7 vaccine and 74% and 75%, respectively, for the JNIH-6 vaccine.

In the classification of disease as verified or not verified according to our criteria, four cases were questionable. One JNIH-6 vaccine recipient and one JNIH-7 vaccine recipient were considered to have possible pertussis and were therefore *not* classified as not verified, because the anti-FHA IgA level was greater than 15 ELISA (enzyme-linked immunosorbent assay) units in both acute or convalescent serum samples.[11] Two JNIH-7 vaccine recipients were considered to be unverified because of a positive culture for *Bordetella parapertussis* and no evidence of pertussis infection other than from FHA serologic study.

COMMENT

There is no single estimate of efficacy for these vaccines. Depending on the severity of clinical symptoms required in the case definition, and whether laboratory confirmation is required, we obtain a wide range of efficacy estimates. This dependence of estimated vaccine efficacy on case definition is one of numerous possible explanations for differing efficacy estimates from different studies.[12]

Efficacy against clinical disease with 28 or more days of coughing spasms and whoops was significantly higher for the JNIH-7 vaccine than for the JNIH-6 vaccine (Table 1). This result may be a chance occurrence or it may be an effect of the larger amount of PT per dose in the JNIH-7 vaccine, if whooping is a PT-associated symptom. There were no significant differences in vaccine efficacy when whoops were not required in a case definition. In an ongoing long-term follow-up of study children, a statistically significant difference has appeared in the opposite direction; efficacy against culture-confirmed pertussis with more than 30 days of cough was higher for the JNIH-6 vaccine than for the JNIH-7 vaccine.[3] Hence, we are unable to conclude that the single-component vaccine had any superiority over the two-component vaccine in protection against long-lasting illness.

For all clinical case definitions used in this analysis, higher vaccine efficacy estimates were obtained when culture confirmation was required. A lower probability of detecting a case (sensitivity) by culture in vaccinated than in unvaccinated children[13] may explain some of this dif-

Table 2.—Clinical Illnesses Not Verified as Pertussis

Case Definition*	Placebo Total	Placebo Complete Data†	Placebo No. (%) Not Verified‡	JNIH-7 Vaccine Total	JNIH-7 Vaccine Complete Data†	JNIH-7 Vaccine No. (%) Not Verified‡	JNIH-6 Vaccine Total	JNIH-6 Vaccine Complete Data†	JNIH-6 Vaccine No. (%) Not Verified‡
21W	46	41	6 (15)	26	21	11 (52)	27	18	6 (33)
28W	35	31	1 (3)	8	5	3 (60)	22	14	5 (36)

*21W and 28W indicate at least 21 or 28 days of coughing spasms with whoops.

†Values represent number with culture and serologic data (including one JNIH-7 vaccine recipient with no serology of, but a positive culture for *Bordetella parapertussis*).

‡"Not verified" values represent number with no evidence of pertussis disease from culture, serologic study, or exposure information, or with a positive culture for *B parapertussis*. Percentage refers to those with complete data.

ference, even though in the Swedish trial such a phenomenon appeared to occur mainly in disease with 21 days or less of coughing spasms.[4] The adjustment of estimated vaccine efficacy for nonpertussis cases suggests that the discrepancy was partially due to nonspecificity of the clinical criteria, as applied in this study. Other adjustment methods—eg, those based on a common estimate of specificity for the vaccine and placebo groups—yield the same qualitative result—that vaccine efficacy is underestimated by clinical case definitions.

One purpose of our analysis was to assess the validity for a future pertussis vaccine trial of a case definition based only on clinical criteria. Use of such a definition could entail less cost and effort than one requiring culture or other laboratory confirmation. A clinical case definition may be appropriate during an investigation of a pertussis outbreak or illness after household exposure, when the intensity of exposure would be relatively high for most individuals.[14] However, we found no clinical case definition that was sufficiently specific for pertussis in the Swedish trial; all of the clinical definitions used led to substantial underestimation of vaccine efficacy. The nonspecificity of clinical case definitions could be partly due to the reliance on parents and study nurses to ascertain disease. However, it was impractical to have a physician investigate each suspected case, and we would expect a similar situation in most large trials.

Similarly, when two vaccines are compared, a case definition with insufficient specificity can lead to considerable bias in the estimation of relative risk of pertussis.[9] If the vaccines have different efficacies, then inclusion of nonpertussis cases will bias relative risk estimates toward 1, tending to make vaccines appear more similar than they actually are. Our analysis suggests that a large proportion of episodes of coughing spasms among vaccinated children were not due to pertussis; this was true even for illnesses with 21 days or more of coughing spasms and whoops. Thus, we would not expect the predictive value for a clinical definition to be much greater than 50% in vaccinees without an unacceptable loss of sensitivity (Table 2). Such a low predictive value and the bias that could result during the estimation of relative risk[9] make a clinical case definition undesirable for a comparison of two pertussis vaccines.

Clearly, a vaccine trial confirmation of suspected pertussis cases is needed. However, the requirement of confirmation solely by culture may be insufficient. Culture may have a different sensitivity in vaccinated and unvaccinated children[4,13] and possibly, although less likely, with different vaccines as well. Moreover, culture lacks sensitivity.[15] Therefore, clinical criteria and culture confirmation should be used together with other laboratory criteria. The most practicable such criteria at present are based on serologic studies. Serologic criteria for diagnosis would have to be carefully determined; the specific criteria used in the Swedish trial, based on intra-assay variability for that laboratory,[4] may not be appropriate in a different setting. Whatever methods are used, it is important that they be chosen carefully, as serologic criteria as well as culture could have different sensitivities and thus introduce bias in the estimation of vaccine efficacy or relative risk.[9]

In future efficacy trials, vaccine efficacy should be estimated both for mild pertussis of short duration and for typical pertussis. For the assessment of efficacy against typical pertussis, a clinical criterion of 21 days or more of coughing spasms seems reasonable for many settings. This criterion is satisfied in 70% to 80% of cases in England and Wales notified to Public Health Laboratory Service, Communicable Disease Surveillance Centre, London, England (Mary Ramsay, MACP, written communication, January 16, 1991), and also appears to correspond to what is considered typical pertussis disease in young children in Sweden and elsewhere.[16,17] Thus, for trials of acellular pertussis vaccines, we suggest the following definition of typical pertussis: 21 days of coughing spasms with confirmation by culture, appropriate serologic techniques, or household exposure to culture-confirmed pertussis (World Health Organization meeting on pertussis case definitions, Geneva, Switzerland, January 10 through 11, 1991). Confirmation by laboratory methods or household exposure makes it unnecessary to require some additional clinical symptom, such as whoops or posttussive vomiting, to make the clinical criteria more specific for pertussis. However, because the sensitivity of either culture or serologic criteria could potentially differ in different vaccine or placebo groups, to determine the most appropriate estimate of vaccine efficacy or relative risk, useful information may be obtained from the estimate calculated with the clinical criteria only and estimates of specificity and predictive value of the clinical criteria (Elizabeth Miller, MB, BS, and Conor P. Farrington, PhD, World Health Organization meeting on pertussis case definitions, Geneva, Switzerland, January 10 through 11, 1991).

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Cynthia G. Last, PhD; Michel Lersen, PhD;
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Sean Perrin, MS (*Arch Gen Psychiatry.* 1991;48:928-934)

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Cheryl Shea Gelernter, PhD; Thomas W. Uhde, MD;
Peter Cimbolic, PhD; Diane B. Arnkoff, PhD;
Bernard J. Vittone, MD; Manuel E. Tancer, MD;
John J. Bartko, PhD (*Arch Gen Psychiatry.* 1991;48:938-944)

Cardiopulmonary Exercise Testing in Children Following Surgery for Tetralogy of Fallot

Teresa L. Tomassoni, PhD; Frank M. Galioto, Jr, MD; Paul Vaccaro, EdD

• The purpose of this study was to compare the cardiopulmonary responses at rest and during exercise of children following surgical correction of tetralogy of Fallot. The physiologic measurements assessed at rest and during maximal treadmill exercise included diffusing capacity of the lung for carbon monoxide, heart rate, oxygen consumption, minute ventilation, and cardiac output. Twenty children with repaired tetralogy of Fallot served as the study group, and 20 normal boys and girls served as controls. Subjects with tetralogy of Fallot had significantly lower values than those of control subjects for maximal cardiac output and somewhat lower values for diffusing capacity of the lung for carbon monoxide and heart rate. We conclude that the exercise cardiac function of children with surgically corrected tetralogy of Fallot is somewhat diminished compared with that of control children. This information is necessary to establish safe, yet effective exercise guidelines for this select population.

(*AJDC.* 1991;145:1290-1293)

Patients with surgically corrected tetralogy of Fallot (TF) have decreased resting mean values for vital capacity, total lung capacity, residual volume, and functional residual capacity.[1] Investigators who have examined the exercise response of children with surgically corrected TF reported abnormal hemodynamics during maximal exercise tests. They also reported a decreased duration in exercise time,[2] a diminished maximal oxygen consumption ($\dot{V}O_2max$),[1,3,4] a depressed cardiac output ($\dot{Q}$),[5] a low work capacity,[6] a low ventilatory threshold,[7] and a low reduced maximal heart rate (HR).[5,6,8] The reason for the decreased exercise capabilities is not fully understood. Early research suggested that the reduced exercise tolerance occurred even though pulmonary blood flow was assumed to be normal. It was attributed to a diminished functional capacity of the myocardium.[9,10] One group suggested that severe pulmonary regurgitation might cause reduced exercise capability.[11] Another group suggested that pulmonary vascular disease caused exercise intolerance in patients undergoing surgical correction of TF,[12] but this has not been supported by catheterization data collected after surgery. No study yet has measured the diffusing capacity of the lung for carbon monoxide (DLCO) during exercise in this population of boys and girls. This study is the first to integrate this parameter with catheterization data.

Based on the exercise responses noted during comprehensive exercise testing, information concerning long-term effects of surgery on exercise tolerance is needed to evaluate the benefits and to prescribe a safe level of recreational activity for patients who have undergone correction of TF. The purpose of this study was to compare the cardiorespiratory responses to exercise testing of control subjects and of patients who had undergone surgical repair of TF.

SUBJECTS AND METHODS

Forty boys and girls between ages 6 and 16 years participated in this study. The study group was composed of 20 patients (nine girls and 11 boys) who were undergoing routine postoperative evaluation for surgically repaired TF. Twenty children (nine girls and 11 boys) approximately matched by age, sex, and body surface area, who were free from any medical disorders and who were not participating in any physical training, volunteered to serve as control subjects. The purpose and procedures of this investigation were explained to the participants and their parents. Written informed consent was obtained for all the children, and the study was approved by the Institutional Human Subjects Review Board, of the Georgetown University Children's Medical Center in Washington, DC.

Laboratory Procedures

All exercise testing was performed in a medically equipped Exercise Physiology Laboratory of the Children's Medical Center. Graded exercise testing was performed on a motor-driven treadmill (Q-55, Quinton Instrument Co, Seattle, Wash). Blood pressure was measured with a mercury sphygmomanometer and a 12-lead electrocardiogram was obtained with a Quinton Q3000 controller. Each subject was allowed ample time to become familiar with breathing through a mouthpiece with a noseclip in place. The exercise protocol was a continuous multistage procedure with three minute stages. Children aged 8 years and older performed a standard Bruce protocol; younger children performed a modified version of this protocol, which consisted of two additional initial stages composed of 2.72 km at 0% grade and 2.72 km at 5% grade.

A medical gas analyzer (Marquette Gas Analysis Corp, St

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From the Division of Pediatric Cardiology, Georgetown University Children's Medical Center, Washington, DC, (Drs Tomassoni and Galioto) and the Department of Physical Education, University of Maryland (College Park) (Dr Vaccaro).

Reprint requests to the Division of Pediatric Cardiology, Georgetown University Children's Medical Center, 3800 Reservoir Rd NW, Washington, DC 20007-2197 (Dr Tomassoni).

Table 1.—Physical Characteristics of Subjects*

Variable	Tetralogy of Fallot	Controls
Age, y	9.93 ± 2.88	10.22 ± 2.48
Height, cm	136.07 ± 19.55	139.98 ± 13.52
Weight, kg	32.81 ± 12.35	35.75 ± 11.47
Body surface area, m^2	1.12 ± 0.28	1.17 ± 0.23

*Values are given as mean ± SEM.

Table 2.—Catheterization Data for Subjects With Tetralogy of Fallot*

Subject No.	Intracardiac Pressures RA	RV	PA	LV	Angiography
1	3	60/4	20/8	. . .	Dilated, well-contracting RV
2	2	30/2	30/2	118/3	Dilated, fair RV contractility
3	3	30/6	26/10	120/80	Poor RV contractility
4	. . .	40/8	22/5	115/8	Normal RV contractility
5	5	46/8	32/8	115/. . .	Normal contractility
6	1	50/13	32/2	120/5	Good LV contractility
7	3	45/3	20/6	96/6	Left and right branch PS
8	2	42/5	24/4	100/. . .	Good RV and LV contractility
9	3	60/5	17/5	. . .	Good RV and LV contractility
10	3	30/5	30/10	100/. . .	Good RV contractility
11	2	30/4	20/5	110/6	Normal RV and LV contractility
12	. . .	70/. . .	20/8	. . .	. . .
13	2	60/3	15/5	120/0	Normal LV contractility
14	5	30/5	30/5	. . .	Good RV and LV contractility
15†	3	110/8	70/10	. . .	Good RV contractility
16	4	40/5	20/8	100/15	Good RV and LV contractility
17	2	35/0	25/0	95/. . .	Good RV and LV contractility
18	3	30/3	20/5	95/6	Diminished RV and LV contractility
19	3	60/4	. . .	. . .	Good RV contractility
20	2	40/5	24/8	100/10	Good RV and LV contractility

*LV indicates left ventricular; PA, pulmonary artery; PS, pulmonary stenosis; RA; right atrial, and RV, right ventricular.

†Surgical repair with conduit; all other patients had transannular outflow patches.

Louis, Mo 1100 Mass Spectrometer) and a pneumotachograph differential pressure transducer interfaced with a specially programmed minicomputer were used to measure gas concentrations for determination of respiratory variables. Baseline values for $\dot{Q}$ and DLCO were measured with the acetylene rebreathing method.[13-15]

During the exercise test, the blood pressure, HR, and electrocardiogram were monitored continuously. The subjects were encouraged to continue to exercise as long as possible to achieve maximal treadmill performance. At maximal exercise, measurements of each of the previously mentioned parameters were repeated. When testing was complete, these parameters were monitored for 5 minutes to provide for an adequate recovery period.

Statistical analysis consisted of Student's *t* tests to probe for significant differences between the control subjects and patients with TF in physiologic parameters measured at rest and at peak exercise. A *P* value of less than .05 was considered significant, and *P* value of less than .10 was suggestive of a trend. Physiologic measurements are presented as means±SEMs.

RESULTS

There were no significant differences in age, height, weight, or body surface area between the TF group and the control group (Table 1).

The 20 patients with TF had undergone surgery 2.0 to 12 years earlier (mean, 6.9 years) at a mean age of 34.7 months. Nineteen patients had right ventricular outflow tract reconstruction, which required a patch that extends across the pulmonary valve annulus. One patient had a conduit to establish continuity between the right ventricle and pulmonary artery. An electrocardiogram and echocardiogram revealed that all 20 patients had right bundle branch block and mild to moderate pulmonary insufficiency, respectively. Catheterization data are presented in Table 2. None of the subjects was symptomatic and all participated in regular physical education class in school.

There were no significant differences between the TF group and the control group in resting $\dot{V}O_2$, minute ventilation, $\dot{Q}$, DLCO, and HR (Table 3).

There were no significant differences between the two groups in peak exercise measures of $\dot{V}O_2$ and minute ventilation ($P>.05$) (Table 4). The mean peak exercise $\dot{Q}$ in the TF group was significantly lower than in the control group ($P<.05$). The DLCO and HR were suggestive of significance ($P<.10$).

Further statistical analyses were performed on the two groups after omitting six subjects, all of whom had high right ventricular pressures indicating residual pulmonary stenosis after repair of TF. By omitting these patients, the peak DLCO levels were significantly lower in the subjects with TF than in the control group ($P=.05$), while the difference in peak $\dot{Q}$ failed to reach significance ($P=.06$). These results indicate that residual problems with lung diffusion and $\dot{Q}$ exist even in those patients who are believed to have good operative results.

COMMENT

Postoperative catheterization data have demonstrated normal $\dot{Q}$ at rest in subjects with TF, provided that the repair has been technically successful.[5,16] Few studies have examined the $\dot{Q}$ response to exercise in subjects following surgical repair of TF. Those studies that are available support our finding of a lower $\dot{Q}$ in patients with surgically corrected TF than in healthy children.[1,3,5,8] Most catheterization-based studies did not evaluate patients during maximal activity. Some studies have revealed abnormal right heart hemodynamic responses at moderate exercise levels.[16,17] In this study, our data revealed poor $\dot{Q}$ dynamics in children after repair of TF during maximal treadmill exercise, while there were no detectable abnormalities at rest.

The mechanisms responsible for the diminished $\dot{Q}$ in patients with TF appear to be multidimensional and complex. Many patients who have undergone surgical repair of TF often develop significant pulmonary insufficiency

Table 3.—Group Means for Resting Physiologic Measurements*

Variable	Tetralogy of Fallot	Controls	*P*
$\dot{V}O_2$, L/min	0.23±0.02	0.27±0.02	.12
$\dot{V}O_2$, mL/kg per minute	7.91±0.81	8.59±1.14	.63
VE, L/min	10.82±0.52	9.55±0.70	.15
$\dot{Q}$, L/min	3.02±0.17	3.04±0.16	.94
DLCO, mL/mm Hg per minute	10.22±0.71	9.65±0.54	.53
RHR, beats per minute	94.1±2.16	92.9±2.44	.73

*Values are given as mean±SEM. $\dot{V}O_2$ indicates oxygen consumption; VE, minute ventilation; $\dot{Q}$, cardiac output, DLCO, diffusing capacity of the lung for carbon monoxide; and RHR, resting heart rate. N=20 except for control subjects' values of $\dot{V}O_2$ and VE.

Table 4.—Group Means for Peak Exercise Physiologic Measurements*

Variable	Tetralogy of Fallot	Controls	*P*
$\dot{V}O_2$, L/min	1.11±0.11	1.29±0.05	.17
$\dot{V}O_2$, mL/kg per minute	34.10±2.98	37.53±2.45	.38
VE, L/min	35.64±2.64	39.46±2.06	.26
$\dot{Q}$, L/min	6.11±0.42	7.51±0.44	.03
DLCO, mL/mm Hg per minute	14.01±0.88	16.14±0.81	.08
PHR, beats per minute	173.8±4.6	184.5±2.9	.056

*Values are given as mean±SEM. $\dot{V}O_2$ indicates oxygen consumption; VE, minute ventilation; $\dot{Q}$, cardiac output; DLCO, diffusing capacity of the lung for carbon monoxide; and PHR, peak heart rate. N=20 except for measures of $\dot{Q}$ and DLCO in the subjects with tetralogy of Fallot and $\dot{V}O_2$ and DLCO in control subjects.

across the reconstructed right ventricular outflow tract, thereby causing increases in right ventricular volume at rest and during exercise.[5,18] This elevated volume will magnify the right heart's filling pressure abnormalities as systemic venous return increases during exercise.[16] With resting elevation in end-diastolic volume in the right ventricle already using the Starling principle of cardiac reserve, further rises do not produce increases in stroke volume during exercise. Stroke volume also depends partially on the afterload resistance against which the ventricle must pump. Any residual pulmonary stenosis, which is often present in patients with TF, will increase this afterload. Inability to increase stroke volume during physical exertion inhibits the ability to increase $\dot{Q}$.[17] It has been demonstrated that in response to exercise of moderate intensity requiring a similar $\dot{V}O_2$, children with TF have higher arteriovenous oxygen differences than healthy children, thus compensating for the lower $\dot{Q}$.[8]

The mean maximal $\dot{V}O_2$ value in the control group was slightly lower than values in healthy children reported by other investigators, as summarized by Krahenbuhl et al.[19] The $\dot{V}O_2$max in the summary ranged from 1.25 L/min for 8-year-old children to 3.14 L/min for 15-year-old adolescents (33.4 to 63.2 mL/kg per minute). Other longitudinal studies have reported data for $\dot{V}O_2$max ranging from 42 to 56 mL/kg per minute for 7- to 15-year-old subjects.[20-24]

The mean maximal exercise $\dot{V}O_2$ value of patients with TF was not significantly different from that of the controls. This finding does not agree with some early reports that found lower exercise $\dot{V}O_2$ values in patients operated on for TF,[3,5,11,25] but it does agree with a recent study that did not find reduced $\dot{V}O_2$ values in children operated on for TF.[8] That recent study attributed the better $\dot{V}O_2$ response to the earlier age of primary repair and fewer residual defects.[8] All of the children in our study were operated on at or before the age of 6 years and had few residual defects, except for pulmonary insufficiency excluding one patient with residual obstructive problems who required another operation.

It is very difficult to compare our values for maximal exercise DLCO with those of others who have assessed DLCO in healthy children because different methods have been used to measure this variable. One previous study used the acetylene-helium rebreathing method to measure DLCO during exercise in children. A mean peak DLCO of 16.08 mL/mm Hg per minute (ranging from 12.87 to 20.47 mL/mm Hg per minute) was reported for healthy children aged 6 to 17 years.[26] No studies have been found that have measured maximal exercise values for DLCO in children following surgical repair of TF.

We believe that the slightly lower maximal exercise DLCO values achieved for patients operated on for TF compared with the controls in our study is due to a primary interstitial interface defect. Several investigators[27-29] have supported this theory of a diminished DLCO in subjects with TF. They suggest that pulmonary vascular changes occur as a result of either a decreased pulmonary blood flow or increased blood viscosity, which leads to thrombosis of small arteries that may form, occluding interstitial fibrotic bands. In our patients, cardiac catheterization following surgery revealed no evidence of pulmonary vascular obstructive disease, but catheterization data do not measure interstitial thickening.

These results emphasize the need to measure more than just $\dot{V}O_2$ in these patients because they have significant problems with DLCO and $\dot{Q}$ while having normal $\dot{V}O_2$.

The mean value for peak HR obtained in our study of the control subjects was slightly higher than that observed in the subjects with TF. It is difficult to compare these data with data in the literature as we report peak HR and only maximal values have been reported in the literature. When the generally accepted criteria for the attainment of the maximal effort are not met, the term *peak* is usually used.[30] In clinically tested children, a plateau of $\dot{V}O_2$ is usually not observed. Therefore, we report peak HR values. The maximal HR of healthy children and adolescents has been reported to range between 195 and 215 beats per minute.[31,32] The finding of a slightly lower peak HR in our subjects with TF compared with the reference group is in general agreement with other studies that have documented reduced maximal HR levels in patients following surgical repair of TF.[4-6,8,33] It has been suggested that this chronotropic limitation may be due to sinus node dysfunction as a result of the preoperative cyanosis.[8] Other explanations implicate pulmonary regurgitation or stenosis.[11] None of the patients who had surgery for TF in this study had severe pulmonary regurgitation, but six had significant residual stenosis.

CONCLUSION

We conclude that the cardiovascular system of children who have had surgery for TF is able to maintain proper functioning with the use of physiologic compensatory mechanisms during resting conditions. When the cardiorespiratory system is stressed by peak exercise, subjects with TF respond adversely because they have already used compensatory mechanisms to maintain normal resting values. The mean maximal $\dot{Q}$ is significantly lower than those of control subjects. Impaired gas exchange, when measured as DLCO during exercise in subjects with TF may be an inherent part of the pathophysiology of the defect or a complication of the palliative and surgical repairs.

This impairment in maximal $\dot{Q}$, DLCO, and HR should be considered when recommending exercise for patients who have been operated on to correct TF. We recommend that patients with impaired $\dot{Q}$ and/or lung-diffusing capacity avoid maximal effort during sports and advise participation in activities of only moderate intensity. Resting values of $\dot{Q}$, DLCO, and HR are deceiving, and the patient should undergo maximal exercise testing before participation in sports, especially on a competitive level.[34] Measurement of $\dot{Q}$, DLCO, and HR at peak exercise may uncover patients with exercise capacity not discerned at rest or on exercise testing that does not include measurements of these parameters.

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Pediatric Germ Cell and Human Chorionic Gonadotropin–Producing Tumors

Clinical and Laboratory Features

*Anna T. Englund, MD; Mitchell E. Geffner, MD; Ronald A. Nagel, MD;
Barbara M. Lippe, MD; Glenn D. Braunstein, MD*

• Germ cell tumors may cause various aberrations in pubertal development. In prepubertal boys, these tumors may secrete human chorionic gonadotropin, resulting in precocious puberty. Human chorionic gonadotropin and α-fetoprotein are both useful as germ cell tumor markers in the diagnosis and detection of recurrence. Pregnancy-specific β_1-glycoprotein, another oncoplacental antigen, has been used as a tumor marker for trophoblastic neoplasms, but not previously for human chorionic gonadotropin–producing tumors associated with precocious puberty. Patients with germ cell tumors may also have abnormal karyotypes. Herein, we describe six male pediatric patients with germ cell tumors and pubertal derangements seen during an 8-year period. We confirm the high incidence of associated sexual precocity, the usefulness of α-fetoprotein, human chorionic gonadotropin, and pregnancy-specific β_1-glycoprotein as tumor markers in the diagnosis and follow-up of these patients, and the occurrence of sex chromosomal abnormalities.

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Germ cell tumors occur rarely in children, but when present, they may cause abnormalities in puberty based on their anatomic location or due to the secretion of human chorionic gonadotropin (hCG). The most common hCG-secreting tumor causing precocious puberty is hepatoblastoma; however, germ cell tumors in various locations have also been reported to cause sexual precocity.[1-6] Human chorionic gonadotropin and α-fetoprotein (AFP) are two tumor markers that have been used in the diagnosis and treatment of these patients. Pregnancy-specific β_1-glycoprotein (SP-1), like hCG, is an oncoplacental protein that has been used as a marker for trophoblastic disease and various other neoplasms.[7,8] However, there are no reports concerning use of SP-1 as a tumor marker in patients with precocious puberty secondary to hCG-producing tumors. We describe six pediatric patients with germ cell tumors seen in our clinic during an 8-year period, in whom the usefulness of these tumor markers was investigated. Because of an association between germ cell tumors and Klinefelter's syndrome,[4,9-11] chromosomal analyses were also undertaken.

PATIENTS AND METHODS

Patients

Between 1983 and 1990, five patients (all male) were referred to both the pediatric endocrinology and hematology services at UCLA Medical Center for evaluation of germ cell tumors with abnormalities in pubertal development. A sixth male patient is included who presented with precocious puberty associated with a hepatoblastoma. The clinical data of these patients are summarized in Table 1 and their laboratory data in Table 2.

Methods

Serum luteinizing hormone (LH) and follicle-stimulating hormone (FSH) concentrations were measured with radioimmunoassay (Amersham Corp, Arlington Heights, Ill). Testosterone was measured with standard radioimmunoassay. α-Fetoprotein was measured using an enzymatic immunoassay (Abbott Laboratories, Abbott Park, Ill); hCG, with an immunoradiometric assay (Hybritech Inc, San Diego, Calif); and SP-1, with radioimmunoassay as previously described.[12] Chromosomal karyotype was determined from peripheral lymphocytes, skin fibroblasts, and bone marrow using trypsin-Giemsa staining. A karyotype test was also performed on tumor tissue from patient 3. Bone age was determined from the standards of Greulich and Pyle.[13]

RESULTS

Patients 2, 3, and 6 clearly had precocious puberty and patient 5 had delayed puberty. While receiving therapy for growth hormone deficiency, patient 1 unexpectedly developed early pubertal changes, prompting an investigation that led to the discovery of his tumor.[3] The testicular volumes were small with respect to the degree of pubertal development in all patients except patient 2. Patients 2, 3, and 4 had germ cell tumors in the anterior mediastinum; patient 5, in the testicle; patient 1, in the

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From the Department of Pediatrics, UCLA Medical Center (Drs Englund, Geffner, Nagel, and Lippe) and the Department of Medicine, Cedars-Sinai Medical Center, Los Angeles, Calif (Dr Braunstein).

Reprint requests to Department of Pediatrics, UCLA Medical Center, MDCC 22-315, 10833 Le Conte, Los Angeles, CA 90024 (Dr Englund).

Table 1.—Clinical Data*

Patient No.	Age, y	Diagnosis	Ht Age,y	Ba, y	Test Vol, mL	Puberty
1	11.4	Suprasellar teratoma	8.8	10	4-5	Precocious; Tanner II
2	10.3	Anterior mediastinal teratoma/choriocarcinoma	11	16	15	Precocious; Tanner V
3	11.3	Anterior mediastinal yolk sac tumor	13	16-17	8-10	Precocious; Tanner V
4	15.9	Anterior mediastinal yolk sac tumor	18+	ND	5-6	Appropriate; Tanner V
5	18.5	L testicular seminoma	15	16	R 4; L 8-10	Delayed; Tanner III
6	1.5	Hepatoblastoma	1.7	1.5	4	Precocious; Tanner II

*Ht Age indicates the age at which the patient's height was at the 50th percentile; BA, bone age; Test Vol, testicular volume; R, right; L, left; ND, not done; and, Tanner, Tanner stage of genital/pubic hair development (II, early puberty; III, midpuberty; and V, adult).

Table 2.—Laboratory Data*

	Patient No.					
	1	2	3	4	5	6
hCG, IU/L						
Preoperative	33	1935	171	<5	100	110
Postoperative	<5	5	<5	ND	<5	6
AFP, μg/L						
Preoperative	<10	454	3000	7400	<4.8	1.1×10^6
Postoperative	ND	2.5	5.2	1.6	<4.8	9.6
SP-1, μg/L						
Preoperative	<5.7	9.95	<5.7	ND	ND	10.9
Postoperative	ND	<5.7	<5.7	ND	ND	<5.7
LH, IU/L†						
Preoperative	25	810	115	26	78	ND
Postoperative	<2	2	16	ND	13	ND
FSH, IU/L						
Preoperative	4	2	<2	39	<2	ND
Postoperative	<2	9	4	ND	48	ND
Testosterone, nmol/L						
Preoperative	18.2	33.6	19.3	3.0	35.0	44.4
Postoperative	<0.3	9.5	7.5	ND	14.5	<0.3
Karyotype	ND	46,XY‡§	46,XY‡§; 49,XXY, +8, +marker‖	46,XY/47,XXY‡	46,XY‡	ND

*hCG indicates human chorionic gonadotropin (normal, 0 to 5 IU/L); AFP, α-fetoprotein (normal, 0 to 6.6 μg/L); SP-1, pregnancy-specific β_1-glycoprotein (normal, <5.7 μg/L); LH, luteinizing hormone (normal adult male, 5.0 to 30 IU/L; prepubertal children, <5 IU/L); FSH, follicle-stimulating hormone (normal adult male, 2.5 to 16 IU/L; prepubertal children, <10 IU/L); and ND, not done. Normal testosterone levels are as follows: adult male, 12.1 to 35.7 nmol/L; prepubertal children, less than 0.3 nmol/L).

†False-positive increases in LH due to hCG.

‡Peripheral lymphocyte karyotype.

§Skin fibroblast karyotype.

‖Bone marrow and tumor tissue karyotype showed 49,XXY with an extra chromosome 8 and unidentified marker chromosomes (see text for explanation).

suprasellar region; and patient 6 had a hepatoblastoma. The bone age was advanced in two patients (patients 2 and 3) and appropriate for age in three others (patients 1, 5, and 6). The serum LH and testosterone levels were elevated before surgery in all patients, and decreased with therapy. The serum FSH level was low initially in all patients, except patient 4, who had Klinefelter's syndrome.

Tumor markers were useful in all patients. The hCG level was elevated in five of the six patients before surgery, and decreased with therapy. Patients 2, 3, 4, and 6 had elevated AFP levels; of the four patients in whom it was measured, SP-1 levels were elevated initially in patients 2 and 6, but decreased after surgery. However, hCG and AFP levels were also elevated in both patients in whom SP-1 was detected. Of the four patients tested, patients 3 and 4 had chromosomal mosaicism consistent with Klinefelter's syndrome. While mosaicism was detected with the routine peripheral lymphocyte chromosomal study of patient 4, the karyotype of patient 3 was normal in both peripheral blood and skin fibroblasts. However, analysis of bone marrow and tumor tissue from patient 3 revealed a mosaic Klinefelter karyotype as well as an additional chromosome 8 and an extra unidentified chromosomal marker. Fifty-six percent of the cells had 49 chromosomes (46,XXY, +8, +marker). Twenty-five cells had 48 chromosomes, all 46,XXY, but half with the +8 chromosome, and the other half with the +marker chromosome. The remaining cells had fewer than 48 chromosomes with similar changes, but random chromosome loss attributed to technical artifact.

COMMENT

Germ cell tumors may occur in the testis or ovary, or in a variety of extragonadal sites.[14] It is believed that the widespread location of germ cell tumors is due to aberrant migration in the fetus. While hepatoblastomas are not traditionally classified as germ cell tumors, reports on the structure of certain hepatoblastomas have shown multinucleated giant cells that stain positively for hCG and are morphologically similar to syncytiotrophoblastic cells.[6,15]

In pediatric patients, germ cell tumors often present with abnormalities in pubertal development. Paraneoplastic precocious puberty is caused by ectopic hormone production by a tumor, ie, hCG. Approximately 4% of boys with precocious puberty have hCG-producing tumors.[5] In a review of 35 cases of paraneoplastic precocious puberty, Navarro et al[4] noted that the most frequent cause was hepatoblastoma, followed by mediastinal teratoma, intracranial germ cell tumors, and, last, presacral and retroperitoneal carcinomas. All our patients had abnormalities in pubertal development. Three had tumors in the anterior mediastinum, while the other lesions occurred in the cranium, the testis, and the liver.

In patients with germ cell tumors, the early development of secondary sexual characteristics is due to stimulation of the testis by hCG causing secretion of testosterone without maturation of the hypothalamic-pituitary-testicular axis. This syndrome occurs almost exclusively in boys, although there have been reports of one affected girl.[16,17] Since hCG has LH-like biological activity (and cross-reactivity with the radioimmunoassay for LH), it is able to induce Leydig cell hyperplasia and testosterone secretion. However, Leydig cells do not constitute more than 25% of total testicular volume in the adult male.[1] Serum FSH levels are generally low in these patients, and therefore fail to stimulate Sertoli cell hyperplasia or spermatogenesis. For these reasons, boys with precocious puberty secondary to hCG production by tumors typically have only mildly enlarged testes, discordant with their degree of pubertal development.[18] Girls with hCG-producing tumors almost never develop precocious puberty, perhaps because the pulsatile secretion of both LH and FSH is required for follicular maturation.[2,4]

In patients with paraneoplastic precocious puberty, tumor markers such as AFP and hCG have been very helpful in diagnosis, monitoring of therapy, and detection of recurrence. α-Fetoprotein is a protein normally synthesized in fetal liver, gastrointestinal tract, and yolk sac; however, the postnatal detection of this protein may be indicative of abnormal secretion by a neoplasm. Human chorionic gonadotropin is normally synthesized by trophoblastic tissue of the placenta during pregnancy.[12,19] In our patients, either hCG or AFP levels were elevated at diagnosis and declined with therapy. Half of our patients had elevations of both tumor markers. We also report our results measuring SP-1, a protein that is normally secreted by the placental syncytiotrophoblast.[7,20] Although the function of SP-1 is not known, the concentration of this protein increases progressively throughout pregnancy until 36 weeks of gestation. Pregnancy-specific β_1-glycoprotein has been very useful as a tumor marker in the diagnosis and treatment of gestational trophoblastic diseases.[7,8,21-25] There have been many conflicting reports regarding the usefulness of SP-1 as a marker in other neoplasms such as testicular and ovarian germ cell tumors. Although many authors have described levels of serum SP-1 that parallel those of hCG, they do not offer any additional information.[17,26-29] However, there have been reports of cases of discordance between levels of serum SP-1 and hCG, suggesting that SP-1 alone can be a specific tumor marker.[30-33]

In our patients with germ cell tumors, the serum SP-1 concentration was elevated before surgery in two of the four patients in whom it was measured, and declined with therapy in both. It is noteworthy that the highest SP-1 level occurred in the patient with hepatoblastoma (patient 6). This supports the suggestion that hepatoblastomas may have syncytiotrophoblastic components. In our four patients in whom it was measured, SP-1 did not appear to have any advantage over hCG or AFP as a tumor marker.

There is a known association between Klinefelter's syndrome and anterior mediastinal tumors that secrete hCG.[4,9-11] Therefore, all our patients with tumors in this location underwent karyotyping. Patient 4, with an anterior mediastinal germ cell tumor, had mosaicism for Klinefelter's syndrome in peripheral blood lymphocytes. Patients 2 and 3, with tumors in this location, had normal chromosomes in peripheral blood and skin fibroblasts. However, patient 3 was shown to have Klinefelter's syndrome with a mosaic karyotype in the bone marrow and the tumor itself. Chromosome studies were not conducted on patients 1 and 6 since their tumor types (suprasellar teratoma and hepatoblastoma) are not known to be associated with karyotypic abnormalities. Thus, it is important to examine the chromosomal karyotype in a variety of tissues in male patients with anterior mediastinal germ cell tumors, regardless of their age or pubertal status.

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The karyotype test on tumor tissue from patient 3 was performed by Nancy Wang, PhD, University of Rochester (NY) Medical School.

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SPECIAL FEATURE

Radiological Case of the Month

William G. Bennett, MD (Contributor), *Beverly P. Wood, MD* (Section Editor)

A white boy born at 35 weeks' gestation was referred to Childrens Hospital of Los Angeles at age 4 days for evaluation of a mass palpated on the left side of the abdomen. The patient's mother was a gravida 1, para 1, 26-year-old whose prenatal course was complicated by gestational diabetes that was controlled with diet alone until 5 weeks before delivery, when it became necessary for her to self-administer subcutaneous insulin daily. Two days before admission, fetal movement ceased. On the second day of absent fetal movement, a nonstress test demonstrated mild decelerations in fetal heart rate thought to be secondary to fetal hypoxia. A transuterine ultrasound examination of the fetus was performed and demonstrated a mass in a left suprarenal location. On cesarean section, a 3600-g jaundiced boy was delivered.

The 1-minute and 5-minute Apgar scores were 7 and 9, respectively. Results of physical examination of the infant demonstrated a palpable left-upper-quadrant mass and jaundice. The total bilirubin level had risen from 200 μmol/L at birth to 320 μmol/L the day after birth and to 280 μmol/L the same day, but after phototherapy. The patient's urine was brown and contained numerous red blood cells. An abdominal ultrasound examination demonstrated a mass with a left suprarenal location displacing the left kidney inferiorly (Fig 1). The cortex of the kidney had hyperechoic streaks, and the pyramids were prominent (Fig 2). The right kidney and adrenal gland were normal.

The patient returned for a follow-up abdominal computed tomographic scan (Fig 3) and renal scan (Fig 4) 3 months after discharge. The left adrenal gland contained a few calcifications. However, the left kidney was markedly atrophic, nonenhancing, and only 2 cm long. The right kidney was normal in size and appearance, and the right adrenal gland was normal. The child was hypertensive but exhibited normal development.

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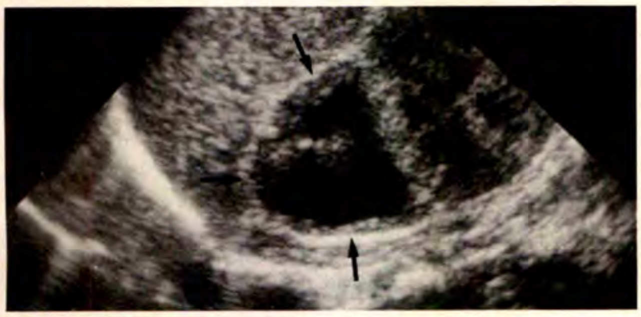
Contributed from the Department of Radiology, Arkansas Children's Hospital, 800 Marshall St, Little Rock, AK 72202.

Reprint requests to the Department of Radiology, Box 81, Childrens Hospital of Los Angeles, 4650 Sunset Blvd, Los Angeles, CA 90054-0700 (Dr Wood).



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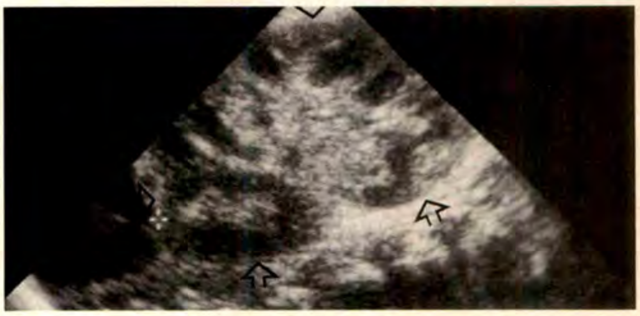

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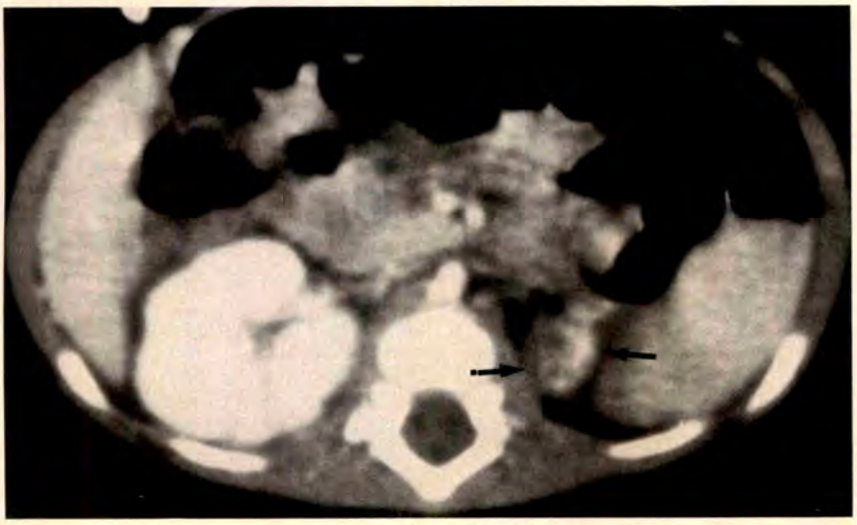

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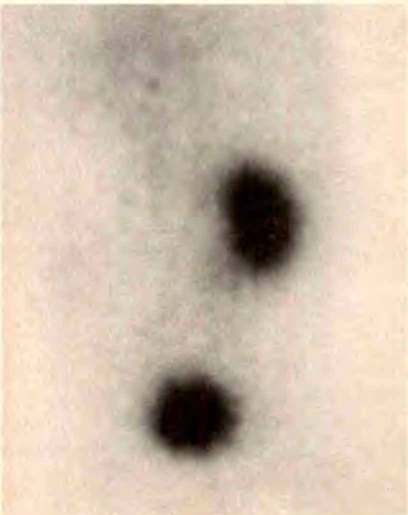

Figure 4.

Denouement and Discussion

Left Renal Vein Thrombosis and Left Adrenal Hemorrhage

Fig 1.—*Ultrasonogram of left suprarenal region shows mass with solid rim (arrows) and liquefied center.*

Fig 2.—*Ultrasonogram of left kidney (arrows) shows hyperechoic streaks in parenchyma.*

Fig 3.—*Computed tomogram at age 3 months shows tiny, atrophic left kidney (arrows).*

Fig 4.—*Renal scan at age 3 months shows no renal function in the left kidney.*

Adrenal hemorrhage is one of the less common causes of flank mass in neonates, the most common being renal masses such as hydronephrosis or multicystic dysplastic kidney.[1] There is an association between adrenal hemorrhage on the left side and ipsilateral renal vein thrombosis because of the anatomy of the left adrenal vein as a tributary of the left renal vein. Thrombus originating in the left adrenal vein may propagate into the left renal vein and even into the inferior vena cava.[2-4] On the right side, the renal and adrenal veins enter the inferior vena cava separately.

Adrenal hemorrhage in the neonate is associated with an infant who is large for gestational age, a breech delivery, sepsis, trauma, hypotension, hypovolemia, and hypoxemia. The clinical signs of adrenal hemorrhage are jaundice and a flank mass. The corresponding laboratory sign is elevated serum bilirubin values. Hematuria is not a feature of isolated adrenal hemorrhage but indicates renal vein thrombosis. Although the differential diagnosis of an adrenal mass includes neuroblastoma, serial abdominal ultrasound examinations demonstrate a solid adrenal gland followed by progressive central liquefaction and early resorption of adrenal hemorrhage within 2 weeks after birth, with complete resolution in 6 weeks. Adrenal function is unimpaired and residual dystrophic calcification frequently persists after resolution of the hemorrhage. Neuroblastoma increases in size during observation with serial ultrasound evaluation. Magnetic resonance imaging can help distinguish between adrenal hemorrhage and neuroblastoma because hemorrhage exhibits markedly increased signal intensity on T_1- and T_2-weighted sequences due to extracellular methemoglobin present within 72 hours of the acute event and persisting for several weeks afterward as methemoglobin is transformed into hematin, with decreased signal on T_1- and T_2-weighted images. Neuroblastoma exhibits heterogeneous intermediate signal intensity on T_1- and T_2-weighted images without significant change during the same time.

Renal vein thrombosis in the neonate is usually unilateral, and in most instances there is a history of hypoxia, sepsis, hypotension, or severe dehydration. There is an increased association with maternal diabetes, and thrombosis of the left renal vein is also associated with left adrenal hemorrhage. When both kidneys are affected, the infant presents with renal failure. When only one kidney is affected, the infant develops hematuria, proteinuria, and occasionally hypertension. The ultrasound findings vary from a normal appearance to enlargement of the kidney in the early stages, with a streaky increase of parenchymal echogenicity and loss of corticomedullary distinction. Later, results of radionuclide studies reveal poor or absent global renal perfusion, with poor excretion of tracer material. Serial radionuclide studies are helpful in monitoring return of function.

After renal vein thrombosis, the involved kidney may recover function if adequate collateral venous drainage is present or prompt recanalization of the renal vein occurs. If circulatory compromise persists, the involved kidney can respond by increasing renin production with resultant systemic hypertension, or the kidney may involute into an atrophic nonfunctioning kidney, usually without hypertension.

This neonate's adrenal hemorrhage was demonstrated in utero and was likely the result of hypoxia resulting from accelerated placental atherosclerosis in the presence of maternal diabetes. This event probably occurred during the 2 days before the nonstress test. Maternal diabetes and large infant size are predisposing factors in thrombosis of the left renal vein. This baby was large for gestational dates, which is consistent with poor control of maternal blood glucose levels.

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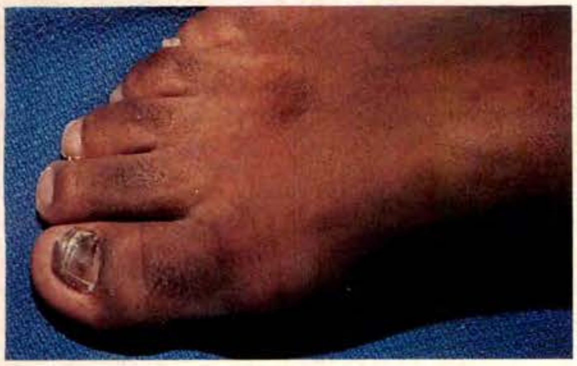
Picture of the Month

Philip R. Cohen, MD, Adelaide A. Hebert, MD (Contributors); *Murray Feingold, MD* (Editor for This Case); *Walter W. Tunnessen, Jr, MD* (Section Editor)

The statements listed below are best associated with which of the figures: (*a*) This is a condition of autosomal-dominant inheritance affecting all nails. (*b*) This is a condition of autosomal-dominant inheritance affecting only one or two nails. (*c*) This is not a hereditary condition and affects all nails.



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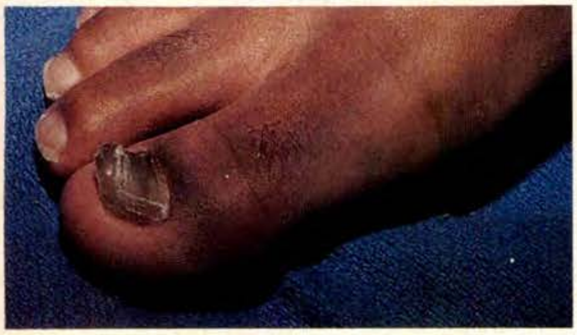

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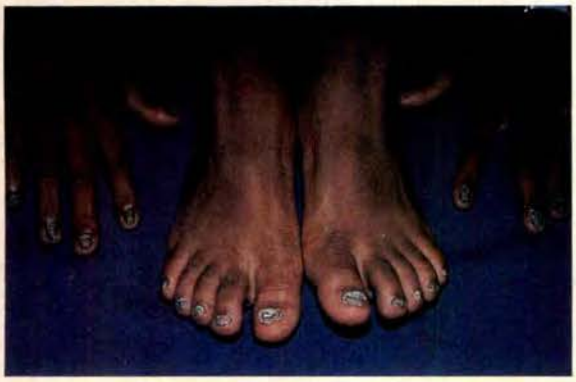

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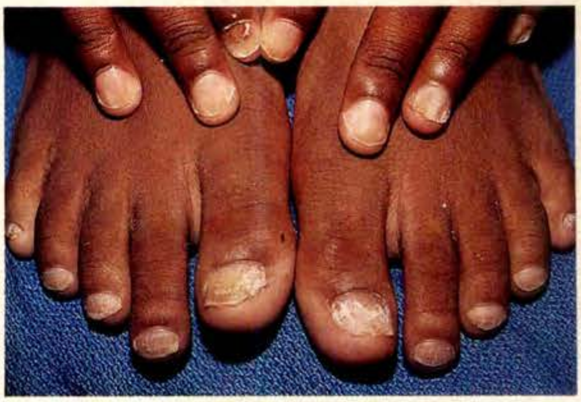

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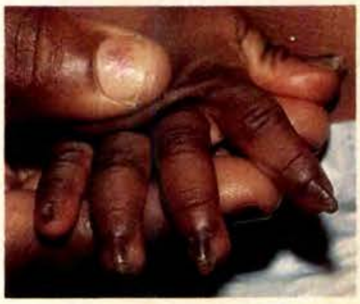

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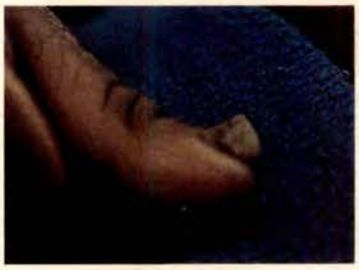

Figure 6.

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Contributed from the Departments of Dermatology (Dr Cohen) and Pediatrics (Dr Hebert), University of Texas Medical School at Houston.

Reprint requests to National Birth Defects Center, Franciscan Children's Hospital, 30 Warren St, Brighton, MA 02135 (Dr Feingold).

Denouement and Discussion

Pachyonychia Congenita

Figs 1 and 2.—*A patient with congenital malalignment of the great toenail in which the right hallux nail is deviated in a lateral direction and has multiple transverse ridges on its surface.*

Figs 3 and 4.—*Thin, friable nails with loss of nail luster, multiple pits, excess longitudinal ridging, and distal notching that splits the nail into layers in a child with 20-nail dystrophy of childhood.*

Figs 5 and 6.—*Distal hypertrophy of the nails with marked subungual hyperkeratosis in a boy with pachyonychia congenita.*

(*a*) Pachyonychia congenita is a rare genodermatosis of autosomal-dominant inheritance with a high degree of penetrance and variable phenotypic expression. This disorder, first described by Jadassohn and Lewandowsky in 1906, has also been referred to as Jadassohn-Lewandowsky syndrome. The onychodystrophy typically appears within the first 6 months of life, and may be present at birth. It is characterized by hypertrophy and distal subungal hyperkeratosis of all nails. Secondary complications include nail shedding, chronic paronychial infections, and increased susceptibility to local traumatic injuries. The only effective treatment of the nail dystrophy has been surgical removal of the entire nail. Radical excision of the nail, nail bed, and nail matrix, followed by vigorous curretage and electrodessication of the bed and matrix with subsequent skin implantation at the site of the removed nail has provided good functional and esthetic results. In addition to onychodystrophy, mucosal and cutaneous manifestations associated with pachyonychia congenita include palmoplantar hyperkeratosis, leukokeratosis of the tongue and oral mucosa, follicular keratosis (especially on the elbows and knees), bullae and erosions on the palms and soles, natal or neonatal teeth, and angular cheilosis. Hair anomalies, corneal dyskeratosis, hoarseness, cataracts, mental retardation, and alopecia are less frequently noted features of pachyonychia congenita.

(*b*) Congenital malformation of the great toenails is an autosomal-dominant inherited onychodystrophy with variable expression that affects the nail of one or both halluces. The disorder is typically present at birth and characterized by lateral deviation of the nail with respect to the long axis of the phalanx. Transverse ridging is often present across the entire surface of the nail, and, less commonly, the nail may be discolored, thickened, shortened and/or onycholytic (characterized by loosening or separation of the nail from the nail bed). Complications of congenital malformation of the great toenails include ingrown toenails and hemionychogryphosis (a hooked or incurved nail). Although spontaneous improvement has been observed in a few children, the disorder usually persists into adulthood if not corrected earlier. Surgical realignment of the entire nail may be necessary for individuals with either marked nail deviation or condition-related disabling sequelae. The clinical differential diagnosis of congenital malformation of the great toenails may be made based on the presence of bacterial and candidal paronychia, ingrown toenails, congenital hypertrophy of the lateral nail folds of the hallux, dermatophyte infection, and onychogryphosis.

The Editors welcome contributions to Picture of the Month *and* Radiological Case of the Month. *Those who wish to contribute should send their manuscripts to Dr Tunnessen (*Picture of the Month*), The Children's Hospital of Philadelphia, 34th Street and Civic Center Blvd, Philadelphia, PA 19104, or Dr Wood (*Radiological Case of the Month*), Department of Radiology, Childrens Hospital of Los Angeles, 4650 Sunset Blvd, Los Angeles, CA 90027. Articles and photographs accepted for publication will bear the contributor's name. There is no charge for reproduction and printing of color illustrations.*

(*c*) In 1977, Hazelrigg et al described six healthy children with an onychodystrophy that uniformly affected the nails of all 20 digits: 20-nail dystrophy of childhood. There was no evidence of psoriasis vulgaris, lichen planus, alopecia areata, dermatitis, or ectodermal defects. Therefore, this condition was assumed to be idiopathic. In 20-nail dystrophy of childhood, the onychodystrophy is asymptomatic and appears insidiously. The nails are characterized by excessive longitudinal striations and loss of nail luster. The nails are thin, fragile, and have distal notching that splits the nails into layers. Regular manicuring and application of nail lacquer are the most effective palliative treatments. Similar features of this nail dystrophy have been noted in patients with lichen planus, alopecia areata, psoriasis vulgaris, and IgA deficiency. Hence, it is perhaps most appropriate to reserve the diagnosis of 20-nail dystrophy of childhood for children with idiopathic onychodystrophy that affects all of the nails.

The descriptive term for rough nails, trachyonychia, should be used when the nail changes traditionally found in 20-nail dystrophy of childhood are present in individuals with dermatologic or systemic illness that has also been associated with similar nail findings or in children or adults in whom less than all 20 nails are involved.

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1. Walson PD et al. Ibuprofen, acetaminophen, and placebo treatment of febrile children. *Clin Pharmacol Ther.* 1989;46:9-17. 2. Data on file, McNeil Consumer Products Company.

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INDICATIONS AND USAGE: PediaProfen is indicated for the reduction of fever in patients aged 6 months and older, and for the relief of mild-to-moderate pain in patients aged 12 years and older.

CLINICAL PHARMACOLOGY: Controlled clinical trials comparing doses of 5 and 10 mg/kg ibuprofen and 10-15 mg/kg of acetaminophen have been conducted in children 6 months to 12 years of age with fever primarily due to viral illnesses. In these studies there were no differences between treatments in fever reduction for the first hour and maximum fever reduction occurred between 2 and 4 hours. Response after 1 hour was dependent on both the level of temperature elevation as well as the treatment. In children with baseline temperatures at or below 102.5°F, both ibuprofen doses and acetaminophen were equally effective in their maximum effect. In those children with temperatures above 102.5°F, the ibuprofen 10 mg/kg dose was more effective. By 6 hours children treated with ibuprofen 5 mg/kg tended to have recurrence of fever, whereas children treated with ibuprofen 10 mg/kg still had significant fever reduction at 8 hours. In control groups treated with 10 mg/kg acetaminophen, fever reduction resembled that seen in children treated with 5 mg/kg of ibuprofen, with the exception that temperature elevation tended to return 1-2 hours earlier.

CONTRAINDICATIONS: PediaProfen should not be used in patients who have previously exhibited hypersensitivity to ibuprofen, or in individuals with all or part of the syndrome of nasal polyps, angioedema and bronchospastic reactivity to aspirin or other nonsteroidal anti-inflammatory agents. Anaphylactoid reactions have occurred in such patients.

WARNINGS: Risk of GI Ulceration, Bleeding and Perforation with NSAID Therapy. Serious gastrointestinal toxicity such as bleeding, ulceration, and perforation, can occur at any time, with or without warning symptoms, in patients treated chronically with NSAID therapy. Although minor upper gastrointestinal problems, such as dyspepsia, are common, usually developing early in therapy, physicians should remain alert for ulceration and bleeding in patients treated chronically with NSAIDs even in the absence of previous GI tract symptoms. In patients observed in clinical trials of several months to two years duration, symptomatic upper GI ulcers, gross bleeding or perforation appear to occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for one year. Physicians should inform patients about the signs and/or symptoms of serious GI toxicity and what steps to take if they occur.

Studies to date have not identified any subset of patients not at risk of developing peptic ulceration and bleeding. Except for a prior history of serious GI events and other risk factors known to be associated with peptic ulcer disease, such as alcoholism, smoking, etc., no risk factors (e.g., age, sex) have been associated with increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less well than other individuals and most spontaneous reports of fatal GI events are in this population. Studies to date are inconclusive concerning the relative risk of various NSAIDs in causing such reactions. High doses of any NSAID probably carry a greater risk of these reactions, although controlled clinical trials showing this do not exist in most cases. In considering the use of relatively large doses (within the recommended dosage range), sufficient benefit should be anticipated to offset the potential increased risk of GI toxicity.

PRECAUTIONS: General: Blurred and/or diminished vision, scotomata, and/or changes in color vision have been reported. If a patient develops such complaints while receiving **PediaProfen**, the drug should be discontinued and the patient should have an ophthalmologic examination which includes central visual fields and color vision testing.

Fluid retention and edema have been reported in association with ibuprofen; therefore, the drug should be used with caution in patients with a history of cardiac decompensation or hypertension.

PediaProfen, like other nonsteroidal anti-inflammatory agents, can inhibit platelet aggregation, but the effect is quantitatively less and of shorter duration than that seen with aspirin. Ibuprofen has been shown to prolong bleeding time (but within the normal range) in normal subjects. Because this prolonged bleeding effect may be exaggerated in patients with underlying hemostatic defects, **PediaProfen** should be used with caution in persons with intrinsic coagulation defects and those on anticoagulant therapy.

Patients on **PediaProfen** should report to their physicians signs or symptoms of gastrointestinal ulceration or bleeding, blurred vision or other eye symptoms, skin rash, weight gain, or edema.

In order to avoid exacerbation of disease of adrenal insufficiency, patients who have been on prolonged corticosteroid therapy should have their therapy tapered slowly rather than discontinued abruptly when ibuprofen is added to the treatment program.

The antipyretic and anti-inflammatory activity of **PediaProfen** may reduce fever and inflammation, thus diminishing their utility as diagnostic signs in detecting complications of presumed noninfectious, noninflammatory painful conditions.

As with other nonsteroidal anti-inflammatory drugs, long-term administration of ibuprofen to animals has resulted in renal papillary necrosis and other abnormal renal pathology. In humans, there have been reports of acute interstitial nephritis with hematuria, proteinuria, and occasionally nephrotic syndrome.

A second form of renal toxicity has been seen in patients with prerenal conditions leading to a reduction in renal blood flow or blood volume, where the renal prostaglandins have a supportive role in the maintenance of renal perfusion. In these patients administration of a nonsteroidal anti-inflammatory drug may cause a dose dependent reduction in prostaglandin formation and may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics and the elderly. Discontinuation of nonsteroidal anti-inflammatory drug therapy is typically followed by recovery to the pre-treatment state.

Those patients at high risk who chronically take ibuprofen should have renal function monitored if they have signs or symptoms which may be consistent with mild azotemia, such as malaise, fatigue, loss of appetite, etc. Occasional patients may develop some elevation of serum creatinine and BUN levels without signs or symptoms.

Since ibuprofen is eliminated primarily by the kidneys, patients with significantly impaired renal function should be closely monitored and a reduction in dosage should be anticipated to avoid drug accumulation. Prospective studies on the safety of ibuprofen in patients with chronic renal failure have not been conducted.

Meaningful (3 times the upper limit of normal), elevations of SGPT or SGOT (AST) occurred in controlled clinical trials in less than 1% of patients. A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of more severe hepatic reactions while on therapy with **PediaProfen**. If abnormal liver tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g. *eosinophilia*, rash, etc.), **PediaProfen** should be discontinued.

Safety and efficacy of **PediaProfen** in children below the age of 6 months has not been established.

Pregnancy: Reproductive studies conducted in rats and rabbits at doses somewhat less than the maximal clinical dose did not demonstrate evidence of developmental abnormalities. However, animal reproduction studies are not always predictive of human response. As there are no adequate and well-controlled studies in pregnant women, this drug should be used during pregnancy only if clearly needed. Because of the known effects of nonsteroidal anti-inflammatory drugs on the fetal cardiovascular system (closure of ductus arteriosus), use during late pregnancy should be avoided. As with other drugs known to inhibit prostaglandin synthesis, an increased incidence of dystocia and delayed parturition occurred in rats. Administration of **PediaProfen** is not recommended during pregnancy.

ADVERSE REACTIONS: The most frequent type of adverse reaction occurring with ibuprofen is gastrointestinal. In controlled clinical trials, the percentage of adult patients reporting one or more gastrointestinal complaints ranged from 4% to 16%.

Adverse reactions occurring in 3% to 9% of patients treated with ibuprofen: nausea, epigastric pain, heartburn, dizziness, rash. *Adverse reactions occurring in 1% to 3% of patients:* diarrhea, abdominal distress, nausea and vomiting, indigestion, constipation, abdominal cramps or pain, fullness of GI tract, headache, nervousness, pruritus, tinnitus, decreased appetite, edema, fluid retention (generally responds promptly to drug discontinuation). Still other reactions (less than 1 in 100) have been reported, and are detailed in the full summary of prescribing information.

DOSAGE AND ADMINISTRATION: Shake well prior to administration.

Fever Reduction in Children 6 months to 12 years of age: Dosage should be adjusted on the basis of the initial temperature level (See CLINICAL PHARMACOLOGY for a description of the controlled clinical trial results). The recommended dose is 5 mg/kg if the baseline temperature is less than 102.5°F or 10 mg/kg if the baseline temperature is greater than 102.5°F. The duration of fever reduction is generally 6-8 hours and is longer with the higher dose. The recommended maximum daily dose is 40 mg/kg.

Mild to moderate pain: 400 mg every 4 to 6 hours as necessary for the relief of pain in adults.

In controlled analgesic clinical trials, doses of ibuprofen greater than 400 mg were no more effective than 400 mg dose.

HOW SUPPLIED: PediaProfen Ibuprofen Suspension 100 mg/5 ml (teaspoon)—
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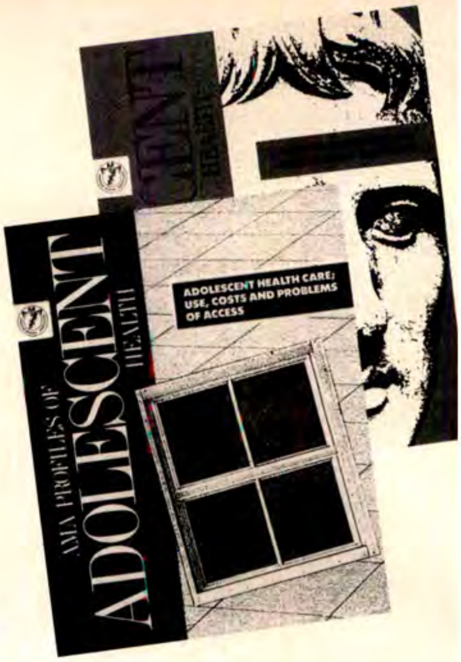

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Direct Bilirubin Measurements in Jaundiced Term Newborns

A Reevaluation

Thomas B. Newman, MD, MPH; Sylvia Hope, PhD; David K. Stevenson, MD

• To investigate the usefulness of measuring direct bilirubin in jaundiced term newborns, we reviewed the outcome of 5255 such measurements on 2877 term (37 weeks' gestation) newborns in two hospitals. Direct bilirubin tests were ordered 15 times as often per infant at the University of California, San Francisco, as at Stanford (Calif) University, and the reported results were more than twice as high. In most of the 149 infants with high (>95th percentile) direct bilirubin levels, the high levels remained unexplained (52% of cases) or were due to apparent laboratory errors (21% of cases). Forty infants (27%) had conditions sometimes associated with high direct bilirubin levels. Elevation of direct bilirubin levels contributed to the diagnosis in only four of these infants. All had minor laboratory abnormalities that resolved spontaneously. Because of their low yield and poor specificity, direct bilirubin tests are seldom helpful in evaluating jaundice in term newborns.

(*AJDC.* 1991;145:1305-1309)

The evaluation of jaundice in newborns is one of the most common tasks in pediatrics. Many authorities recommend measuring the serum direct bilirubin in significantly jaundiced infants to distinguish between conjugated and unconjugated hyperbilirubinemia; algorithms for differential diagnosis of jaundice commonly begin with this step.[1-6] However, the "direct bilirubin" reported by many automated chemical analyzers may be a poor measure of the infant's actual conjugated bilirubin.[7-14]

Although the two terms are often used synonymously, *direct bilirubin* is not the same as *conjugated bilirubin*. Direct bilirubin refers to the bilirubin that reacts directly with diazotized sulfanilic acid (ie, without addition of an accelerating agent) in commonly used chemical assays. Conjugated bilirubin refers to bilirubin that has been made water soluble by binding with glucuronic acid in the liver. The amount of bilirubin that is called direct reacting depends on the concentration of conjugated bilirubin, but also on other factors, including the amount of time it is allowed to react, the concentration of various reagents, and the concentration of unconjugated bilirubin.[8] Unfortunately, in contrast to total bilirubin, for which interlaboratory standardization is available through the College of American Pathologists, there is no standardization of direct bilirubin measurements from laboratory to laboratory.

About 10% to 20% of term newborns develop significant jaundice,[15] but only about 0.04% develop pathologic conjugated hyperbilirubinemia.[16] Because direct bilirubin measurements tend to be least accurate in the presence of high unconjugated bilirubin levels, like those commonly found in newborns, measuring direct bilirubin in jaundiced infants could lead to many false-positive results.[17,18] The purposes of this study were to determine how commonly high direct bilirubin levels occur in infants who are and remain apparently well, to determine how commonly elevations of direct bilirubin are associated with previously unsuspected disease, and to develop guidelines for ordering and interpreting direct bilirubin measurements in jaundiced term newborns.

PATIENTS AND METHODS

Database

We used the Combined Patient Experience (COPE) database as the primary data source for this retrospective study. As has been described in previous reports,[19,20] the COPE database was created by merging computerized data from the clinical laboratory information systems, hospital census records, and hospital discharge abstracts at two hospitals: the University of California, San Francisco, Medical Center (UCSF), and the Stanford (Calif) University Medical Center. We supplemented the COPE database with data from the UCSF obstetrics department database and the Stanford Hospital Medical Information System (for length of stay, race, birth weight, and gestational age estimates). For infants born at UCSF in 1986 and 1987, the COPE database includes laboratory tests performed (at UCSF) after hospital discharge; for all other infants, outpatient data were available only by review of medical records.

Infants were included in the study if they were born and dis-

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From the Division of General Pediatrics, Department of Pediatrics (Drs Newman and Hope), the Division of Clinical Epidemiology, Department of Epidemiology and Biostatistics (Dr Newman), and the Robert Wood Johnson Clinical Scholars Program (Dr Newman), School of Medicine, University of California, San Francisco, and the Division of Neonatology, Department of Pediatrics, School of Medicine, Stanford (Calif) University (Dr Stevenson).

Presented at the 31st Annual Meeting of the Ambulatory Pediatric Association, New Orleans, La, April 29, 1991.

Reprint requests to the Division of General Pediatrics, Box 0374, University of California, San Francisco, CA 94143 (Dr Newman).

Table 1.—Demographic Characteristics of Infants Born During the Study Period at Both Hospitals

	University of California, San Francisco		Stanford (Calif) University	
	10/80-9/82	1/86-12/87	1/86-6/87	Total
Total No. of births	2777	3001	5185	**10 963**
Term group				
No. of births at ≥ 37 weeks' gestation (% of all births)	2417 (87)	2614 (87)	4595 (89)	**9626** (88)
Mean ± SD birth weight, g	3427 ± 496	3435 ± 488	3486 ± 507	3457 ± 499
Length of stay, d				
Median	3	2	2	2
95th percentile	8	7	5	7
Race, No. (%) of infants				
White	1088 (45)	889 (34)	2343 (51)	4332 (45)
Asian	338 (14)	601 (23)	322 (7)	1251 (13)
Hispanic	242 (10)	183 (7)	597 (13)	1059 (11)
Black	193 (8)	157 (6)	368 (8)	674 (7)
Unknown/other	556 (23)	784 (30)	965 (21)	2310 (24)

charged during the periods covered by the COPE database: October 1, 1980, to September 30, 1982, and January 1, 1986, to December 31, 1987, at UCSF and January 1, 1986, to June 30, 1987, at Stanford. Premature infants (obstetrician's estimate at the time of maternal admission of less than 37 weeks' gestation) were excluded. Term infants who were small for gestational age and sick infants were not excluded. Based on reviews of medical records and nursery log books, we estimated that the UCSF database was close to 100% complete and the Stanford database was about 97% complete. The project was approved by the human subjects committees of both UCSF and Stanford.

Laboratory Methods

At UCSF, direct bilirubin was measured on either a DuPont Automated Chemical Analyzer (Dupont Instruments, Wilmington, Del) or a Coulter DACOS analyzer (Coulter Electronics, Hialeah, Fla). Both machines use a modification of the Jendrassik-Grof (diazotized sulfanilic acid) reaction; they were calibrated against each other daily. At Stanford, the Kodak Ektachem 700 (Eastman Kodak Co, Rochester, NY) was used. The Ektachem method measures conjugated (rather than direct) bilirubin using a multilayer slide technique. The conjugated bilirubin is assayed spectrophotometrically after it passes through a selective screening layer and complexes with a cationic polymer.[21]

Data Analysis

Our first task was to define what constitutes an abnormal direct bilirubin level. Textbook definitions generally range from 17 to 34 μmol/L.[5(p23),21-25] (To convert from micromoles per liter to milligrams per deciliter, divide the value by 17.10.) However, because the normal range depends on the analytic method used, we selected the maximum direct bilirubin level recorded for each infant, and arbitrarily defined as abnormal those values in the top 5% (of maximum recorded direct bilirubin levels) for their hospital of birth (≥39 μmol/L at UCSF; ≥17 μmol/L at Stanford). For all such infants, we reviewed the computerized laboratory data and medical records to determine the apparent reason (if any) for the elevation, using the following classifications:

Laboratory Error.—To classify an infant's high direct bilirubin level as due to laboratory error, we required that there be no diagnosis of hepatobiliary disease and that any aminotransferase levels measured be normal. Most of the apparent laboratory errors were isolated high values. To be so classified, there could be only a single abnormal value, and normal values at least 8.5 μmol/L less than the abnormal value had to have been obtained within 25 hours before and after the abnormal value. Other apparent laboratory errors were for miscellaneous reasons, including direct bilirubin levels exceeding the total bilirubin level (n = 2), specimens noted by the laboratory to be hemolyzed (n = 2), misplaced decimal points (n = 2), and mislabeled specimen (n = 1).

Associated Conditions.—This group included any infant not meeting the criteria for laboratory error, with either elevation of aminotransferase levels or a discharge diagnosis (confirmed by laboratory data or medical records review) of any significant hepatobiliary, gastrointestinal, renal, hematologic (except polycythemia), cardiovascular, metabolic (except infants of diabetic mothers), or infectious disease. The direct bilirubin was assumed to have potentially contributed to the diagnosis if its abnormality preceded the signs or diagnostic evaluation that led to the diagnosis, unless progress notes unambiguously indicated another reason for the evaluation.

Unexplained.—This group included all other infants. The high direct bilirubin level was considered to have resolved spontaneously if a return to well within the normal range (<90th percentile) was documented or if the infant was followed up in the outpatient clinic for at least 2 months without evidence of associated disease.

RESULTS

Demographic data on the 10 963 infants born at the two hospitals during the study periods are provided in Table 1. Both hospitals serve ethnically diverse populations, have high rates of preterm or low-birth-weight infants, and have short stays for term infants.

Ordering patterns and results for total and direct bilirubin levels are shown in Table 2 and Fig 1. Data for the two UCSF periods were similar and are combined in Table 2. There was a remarkable difference in the laboratory testing patterns of the two hospitals: infants born at UCSF were more than three times as likely to have total bilirubin measured at least once and more than 10 times as likely to have direct bilirubin measured at least once. The total number of direct bilirubin measurements per infant was 15 times higher at UCSF than at Stanford.

The mean, SD, and, in fact, the entire distributions of total bilirubin levels obtained at the two hospitals were practically identical. This surprising result suggests that the more selective total bilirubin testing at Stanford was based on factors other than the degree of jaundice.

In contrast, the median, 90th, and 95th percentiles for direct bilirubin at UCSF were more than twice as high as those at Stanford (for conjugated bilirubin), reflecting the

Table 2.—Measurements of Total and Direct Bilirubin in Term Infants at Two Hospitals*

	University of California, San Francisco (n=5031)	Stanford (Calif) University (n=4595)	Total (n=9626)
No. (%) of term infants with total bilirubin measured at least once	2786 (55)	753 (16)	**3539**
No. (%) of term infants with direct bilirubin measured at least once	2642 (53)	235 (5)	**2877** (30)
Total No. of direct bilirubin tests	4948	307	**5255**
Mean (SD) maximum total bilirubin, µmol/L†	174 (63)	172 (62)	. . .
Maximum direct bilirubin percentiles, µmol/L†			
50	19	7	. . .
75	24	10	. . .
90	32	14	. . .
95	39	17	. . .
99	63	77	. . .

*At Stanford (but not at the University of California, San Francisco) direct bilirubin actually refers to conjugated bilirubin.

†To convert from micromoles per liter to milligrams per deciliter, divide the value by 17.10.

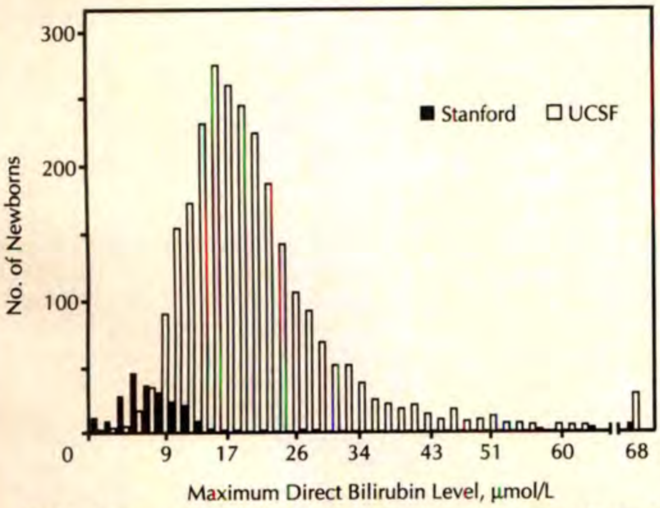

Fig 1.—*Maximum direct bilirubin levels for term infants born at Stanford (Calif) University (1986 to 1987) and at the University of California, San Francisco (UCSF) (1980 to 1982 and 1986 to 1987). To convert from micromoles per liter to milligrams per deciliter, divide values by 17.10.*

different measurement methods. The percentage of total bilirubin that was direct reacting at UCSF was similarly much higher than the percentage of conjugated bilirubin at Stanford.

Medical records were reviewed to determine possible reasons for direct bilirubin levels above the 95th percentile at each institution (Table 3). In most infants, the high direct bilirubin levels remained unexplained (52% of cases) or were due to an apparent laboratory error (21% of cases). Forty (27%) of the 149 infants with high direct bilirubin levels had conditions that are at least occasionally associated with elevated conjugated bilirubin levels. However, the elevated direct bilirubin level did not lead to the diagnosis in any of these infants: most diagnoses were made before the direct bilirubin level was elevated, and most of the elevations were transient and of no apparent clinical significance. Four infants (3%) had findings identified apparently as a result of their direct hyperbilirubinemia. All had minor laboratory abnormalities that resolved spontaneously, including transient, slightly high (50 to 100 U/L) aminotransferase levels in three infants and "sludge" in the gallbladder in one infant.

Table 3.—Reasons for Direct Bilirubin Levels Above the 95th Percentile Among Term Infants at University of California, San Francisco (n=140) and Stanford (n=9)*

Reason	No. (%) of Infants
Unexplained	
Resolved spontaneously, infant well	72 (48)
Well at discharge but no follow-up	6 (4)
Associated disease	
Direct bilirubin did not contribute to diagnosis†	
Isoimmunization	19 (13)
Sepsis or pneumonia	5 (3)
Congestive heart failure	5 (3)
Multiple anomalies	2 (1)
Pyloric stenosis	2 (1)
Extreme SGA, possible rubella‡	1 (1)
Hypothyroid (routine screening)	1 (1)
Choledochal cyst (prenatal sonography)	1 (1)
Direct bilirubin contributed to diagnosis	
Slightly high aminotransferase levels (<100 U/L)	3 (2)
Sludge in gallbladder	1 (1)
Laboratory error	
Isolated high value	24 (16)
Other	7 (5)

*At Stanford (but not at the University of California, San Francisco) direct bilirubin actually refers to conjugated bilirubin.

†Diagnosed from signs or symptoms, except as noted.

‡SGA indicates small for gestational age.

Laboratory errors and unexplained elevations were frequent even at high levels of direct bilirubin (Fig 2). (The graph shows infants only at UCSF because seven of the nine infants at Stanford with maximum direct bilirubin values in the top 5% (for Stanford) had values less than 34 µmol/L) Use of a more restrictive cutoff resulted in little improvement in predictive value: of 30 infants with direct bilirubin values at or above the 99th percentile, only 11 (37%) had possibly associated conditions. Similarly, of 40 infants with direct or conjugated bilirubin levels exceeding the 95th percentile and comprising more than 30% of the total bilirubin, only 17 (42%) had possibly associated conditions. Thus, a more restrictive definition of direct hyperbilirubinemia was still associated with many apparently false-positive results.

We also investigated how often additional laboratory tests were ordered to evaluate direct hyperbilirubinemia. Only 23 (15%) of the 149 infants with high direct bilirubin levels had aminotransferase levels measured; levels were high in three well and 11 sick infants. Five infants received multiple serologic tests for congenital infection (no such infections were found), and three underwent serum protein electrophoresis, the results of which were normal. At least one infant underwent

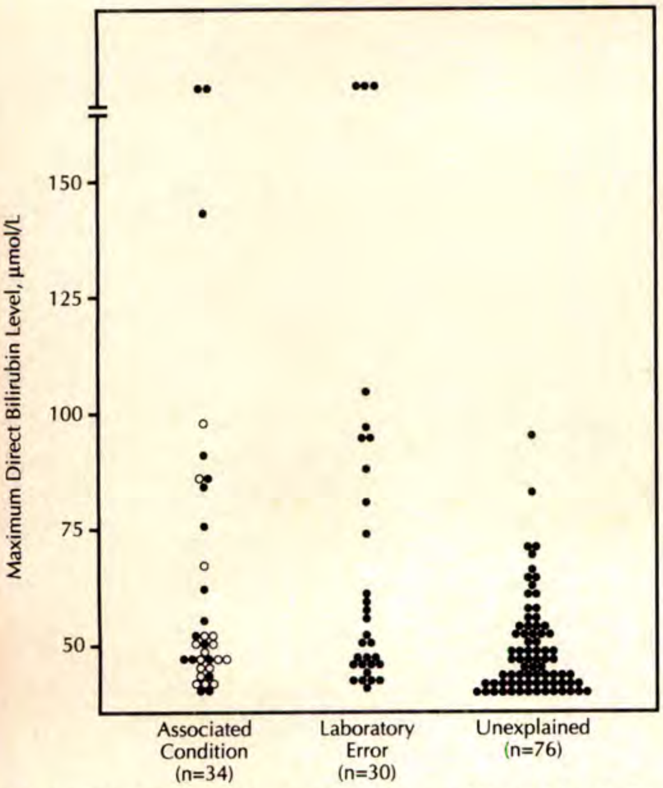

Fig 2.—*Distribution of the maximum direct bilirubin levels for infants born at the University of California, San Francisco (UCSF), with values in the top 5%, by apparent reason for the elevation. Open circles indicate infants in whom the elevation was attributed to isoimmunization; and solid circles, all other infants. To convert from micromoles per liter to milligrams per deciliter, divide values by 17.10.*

abdominal ultrasonography. Thus, additional tests were seldom performed; the usual response to high direct bilirubin levels was either to ignore them or to repeat them until they went down.

COMMENT

The COPE database allowed us to review results of more than 5000 determinations of direct bilirubin on 2877 infants at two hospitals. The striking findings were the marked variation in ordering patterns for this test at the two hospitals, the variation in the median and normal range for the different analytic methods, the high frequency of falsely positive results, and the absence of useful diagnostic information provided.

This study has some important limitations. Tests of direct bilirubin levels were ordered much more commonly at UCSF than at Stanford: the vast majority of infants (140 [94%] of 149) with documented high direct bilirubin levels were from UCSF. Since the analytic method at UCSF is particularly prone to errors, our results may not be generalizable to institutions using better methods. However, in a recent study, the DuPont ACA (used at UCSF) was the most popular machine, in use at 31% of the hospitals surveyed.[10] Clearly, clinicians interpreting results of direct bilirubin determinations need to be aware of the instrument used at their institution, as well as that instrument's accuracy and "normal range."

Our classification system for the high direct bilirubin values was necessarily arbitrary; we cannot say for sure that an isolated high direct bilirubin level was due to laboratory error, or that high values in infants with associated diseases were due to those diseases. However, in developing the classification scheme, we were very restrictive in the laboratory error and unexplained groups, and inclusive in the associated disease group.

This is illustrated by several diagnoses listed in Table 3. Pyloric stenosis, hypothyroidism, and even choledochal cysts are rarely associated with direct hyperbilirubinemia in the newborn period.[26-28] Thus, the elevations of direct bilirubin levels in infants in the associated condition category may have been largely coincidental. Among infants who had direct bilirubin measured, high values were only slightly more common in infants with a discharge diagnosis that would have qualified them for the associated condition category (97 [7.0%] of 1380 infants) than in infants with no such diagnosis (52 [3.5%] of 1497 infants). By including even questionable diagnoses in the associated disease category, we were giving the direct bilirubin measurement the benefit of the doubt in each case.

Similarly, in determining whether high direct bilirubin levels contributed to diagnoses, we required only that they could have contributed, not that they actually did. We were looking for instances in which direct bilirubin measurements led to diagnoses of unsuspected disease. Out of more than 5000 measurements of direct bilirubin, we found no such instances.

This study was limited to term infants, and most of those studied were well. It is likely that in a sicker population, a much greater proportion of the elevations of direct bilirubin would represent significant disease. For example, Wolf and Pohlandt,[29] in a recent case-control study of infants receiving parenteral nutrition, found that cholestasis (bilirubin levels >68 μmol/L with direct bilirubin levels >40% of the total) was strongly associated with sepsis. It apparently was not an early sign, however: the median time between onset of sepsis and cholestasis was about 7 days. Furthermore, although the method of measuring the direct bilirubin was not stated, the absence of elevated values in the control group suggests that it was measured more accurately than has been the case at UCSF.

Although this study included several thousand infants, it could still miss rare, treatable causes of direct hyperbilirubinemia. For example, it is not surprising that we did not find any cases of biliary atresia; its incidence is only about 1 in 10 000.[16] To be useful as a screening test for a disease that rare, however, the measurement of direct bilirubin would need to be much more specific. To have even a 10% positive predictive value would require a specificity of 99.9%, even if the test were 100% sensitive. Furthermore, because most cases of biliary atresia are not associated with cholestasis in the first few days of life,[16] direct bilirubin measurements would be insensitive as well as nonspecific. Finally, the prognosis for biliary atresia does not appear to worsen unless the diagnosis and surgery are delayed more than 2 months.[30,31] Thus, measurement of direct bilirubin in infants remaining jaundiced beyond the first week or two of life would be a more efficient strategy for detecting biliary atresia.

We do not know why tests of direct bilirubin were ordered so much less frequently at Stanford than at UCSF. While the charges for the test differed ($38 at Stanford vs $6 at UCSF), we doubt that the difference in frequency was due to the difference in charges. Rather, it is probably due to shorter stays at Stanford (leading to jaundice being noted in fewer infants), to differences in who decides to order the test (almost exclusively nurses and house staff at UCSF, compared with private pediatricians in about half the cases at Stanford), and differences in nursery traditions at the two institutions. At UCSF (before this study), tests of total and direct bilirubin were almost always ordered together, because treatment decisions were often based on the level of serum indirect bilirubin (ie, the total bilirubin level minus the direct bilirubin level), a practice recommended in many textbooks.[5,25,32]

Is this practice justified? We think usually not. Although automated analyzers provide a value that can be subtracted from the total bilirubin, it is a number that may have little relation to the infant's actual level of conjugated bilirubin. (Interestingly, the Kodak Ektachem, used with admirable restraint at Stanford, is one of the few machines that actually provides a good estimate of conjugated bilirubin.[8,13]) Thus, unless the test used provides an accurate reflection of conjugated bilirubin, treatment decisions should be based on total bilirubin and other evidence of cholestasis (eg, light stools or bilirubin in the urine).

In sick, jaundiced infants, or in any infants in whom cholestasis is suspected, measurement of serum direct bilirubin may be useful. Even then, however, visual examination of the stool and use of a dipstick in the infant's urine[33] may be as good. The infant's kidney can fractionate bilirubin better than most automated chemical analyzers.

Measurement of direct bilirubin is a poor screening test. Clinically inapparent, treatable causes of direct hyperbilirubinemia are rare, and many current methods of measuring direct bilirubin are inaccurate, leading to a high frequency of false-positive results. The practice of ordering a direct bilirubin test to make treatment decisions based on the indirect bilirubin level also generally cannot be justified unless the measurement of direct bilirubin is known to reflect conjugated bilirubin accurately. Our results suggest that measurements of direct bilirubin to evaluate jaundice in term newborns could be drastically reduced with no adverse effect on health.

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Bone Mineral Content of Healthy, Full-term Neonates

Effect of Race, Gender, and Maternal Cigarette Smoking

Pankaja S. Venkataraman, MBBS, James C. Duke, PhD

• In 238 healthy, full-term infants, we evaluated the effects of race, gender, and maternal cigarette smoking on the newborn radial bone mineral content. Sixty-one percent of the infants were male and 39% were female; 161 of 238 mothers were nonsmokers and 77 mothers were cigarette smokers. Bone mineral content was significantly correlated with birth weight, length, and head circumference. There were no significant race- and gender-related differences in neonatal bone mineral content. There was no significant difference in the bone mineral content, bone width, and bone density of the newborn at the left distal-third radius site among the infants of smokers compared with those of nonsmokers, and there was no correlation between neonatal bone mineral content and the number of cigarettes reportedly smoked per day by the mother.

(*AJDC*. 1991;145:1310-1312)

In a report from the United Kingdom in which the bone mineral content of the left forearm was measured, no significant differences were detected between Asian and white singleton newborns of greater than 35 weeks' gestational age and those of less than 2 weeks' postnatal age.[1] In reports from the United States, the bone mineral content of children has been shown to differ with race and gender,[2,3] with lower bone mineral content being observed in female children and in white children. However, we know of no studies that address the issue of whether such differences occur at birth.

The effect of cigarette smoking on the skeleton is varied. Smoking has been reported as a risk factor for development of osteoporosis in some studies,[4-13] but not in others.[14-17] In one study, bone mineral content of the radius was not significantly different between smokers and nonsmokers.[18] However, there was a significantly decreased response to menopausal hormonal therapy in smokers compared with nonsmokers.[19] The possible effects of maternal cigarette smoking on the bone mineral content of the neonate are not known. Hence, in healthy, full-term infants, we evaluated the hypothesis that bone mineral content at birth would be (1) higher in black infants than white infants, (2) higher in male infants than female infants, and 3) lower in infants born to cigarette smokers than in those born to nonsmokers.

SUBJECTS AND METHODS

Two hundred thirty-eight healthy, full-term infants delivered at Oklahoma Memorial Hospital, Oklahoma City, were studied. Informed consent was obtained from a parent in accordance with the University of Oklahoma Institutional Review Board regulations. All infants had weights appropriate for their gestational ages[20] and were free of major congenital malformations. History of maternal smoking was based on the mother's report of having smoked at least 10 cigarettes per day during pregnancy. All infants were studied during the first week of life, and bone mineral content was determined at the distal third of the left radius.

Sixty-one percent of the infants were male, and 39% were female. Race was assigned on the basis of parental identification; when there was ambiguity, data for these infants were excluded from analysis of race effects.

Bone mineral content was determined by photon absorption densitometry with the use of the single photon absorption densitometer (Lunar Radiation, Madison, Wis). The distal third of the left radius was scanned.[21-23] The coefficient of variation of the method is less than 7%.

Bone mineral content and bone width were measured, and bone density was computed as bone mineral content-bone width ratio.

Birth weights, lengths, and head circumferences were measured in all infants. The relationship of body weights and lengths to bone mineral content was also evaluated.

The data obtained were analyzed by means of *t* tests, Pearson's correlations, and regression analyses.[24] The SAS software was used. All data are given as mean±SD. Power was assessed for differences in bone mineral content between white male and female infants, black male and female infants, and infants born to cigarette smokers and nonsmokers.

RESULTS

Birth weights in male and female infants were 3,235±374 and 3208±353 g; length, 50.72±2.69 and 50.47±2.22 cm; and head circumference, 34.06±1.49 and 34.41±1.37 cm, respectively.

In all infants, bone mineral content at birth was positively correlated with birth weight, length, and head circumference with $r = .36$, $P < .0001$ for body weight;

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From the Department of Pediatrics, University of Oklahoma Health Sciences Center, Oklahoma City.

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Reprint requests to Department of Pediatrics, University of Oklahoma Health Sciences Center, PO Box 26901 (2B307/CHO), Oklahoma City, OK 73190 (Dr Venkataraman).

Table 1.—Bone Mineralization in the Term Newborn Infant: Effect of Race and Gender*

	Infant Group			
	White Male	White Female	Black Male	Black Female
N	65	51	50	23
Bone mineral content, g/cm	0.099 ± 0.027	0.094 ± 0.024	0.095 ± 0.022	0.091 ± 0.028
Bone width, cm	0.505 ± 0.123	0.479 ± 0.147	0.496 ± 0.108	0.513 ± 0.130

*Bone mineral content was not significantly different among black and white infants, nor by gender. Infants whose race could not clearly be defined are excluded here (hence the numbers given do not total 238).

Table 2.—Bone Mineral Content in Infants Categorized by Maternal Cigarette Smoking *

	Smokers (n=77)	Nonsmokers (n=161)
Bone mineral content, g/cm	0.098 ± 0.026	0.095 ± 0.025
Bone width, cm	0.502 ± 0.132	0.501 ± 0.127
Bone density, g/cm^2	0.194 ± 0.031	0.194 ± 0.038

*Bone mineral content, bone width, and bone density were not significantly different between the groups.

$r = .24$, $P < .0003$ for length at birth; and $r = .26$, $P < .0009$ for head circumference.

At the left distal-third radius site, the bone mineral content in male and female infants was 97.6±0.2 and 93±0.3 mg/cm, respectively (not significant). No significant differences were noted when infants were subgrouped by race. Bone mineral content and bone width were not significantly different between male and female infants at birth, or between white and black infants (Table 1).

There was no significant difference in bone mineral content, bone width, and bone density among infants delivered to smokers vs those of nonsmokers (group *t* test) (Table 2). Also, neonatal bone mineral content was not significantly correlated by regression analysis with the number of cigarettes smoked prenatally by the mothers.

The power assessment was computed based on a *P* value of .05 with β assumption of .1. For the data obtained in the present study, the power assessment for differences in mineral content between white male and female infants was 93%, that between black male and female infants, 90%; and that between infants born to smokers vs nonsmokers, 91%. The average power for all comparisons was 89%.

COMMENT

Previous studies in adults have documented the gender and racial[25,26] differences in bone mineral content and rate of bone loss with age. In a study of women aged 30 to 80 years, black women were found to have higher total body calcium content and higher radial bone mineral content than white women. The higher total body calcium content was observed even when corrections were made for body size.[27]

The skeletal development of black children has been reported to be advanced compared with that of white children, and body size is greater in black children than white children until adolescence.[26,28-30] In a study of skeletons, the bone density of skeletons from black Americans was found to be higher than that of age-matched white subjects,[31] and osteoporosis is less common in black than white subjects.[32-36]

Although in older children bone mineral content is higher in blacks than whites, and in male vs female children between the ages of 1 and 6 years,[2,3] it was previously unclear whether such differences exist at birth in healthy, full-term infants. In the present study, we found that the bone mineral content at birth did not differ significantly between white and black infants delivered at term gestation. Also, bone mineral content was not significantly different at birth among male and female infants. These findings suggest that although race- and gender-based differences in bone mineral content become apparent in the older child and in the adult, the in utero mineralization of the fetus is not significantly influenced by its race or gender. Our findings are consistent with those of previous reports from the United Kingdom in which there were no significant differences in radial bone mineral content as determined by photon absorption densitometry between white and Asian newborn infants,[1] suggesting that in those groups, ethnic differences are not present at birth.

Smoking has been suggested to decrease intestinal calcium absorption[18] and predispose to the development of skeletal demineralization.[4-13] Hence, smoking may influence the maternal skeleton and, indirectly, that of the offspring. In this study we determined that, in full-term infants, bone mineralization as determined at the distal-third radius site is not significantly altered by maternal cigarette smoking.

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Correction

Incorrect Dose In the article entitled "Intraosseous Infusion of Dobutamine and Isoproterenol," published in the February issue of *AJDC* (1991;145:165-167), an error was made in the "Materials and Methods" section. On page 165, the first line of the fourth paragraph, in the right column, should have read as follows: "Dobutamine and isoproterenol were delivered at rates of 20 and 0.1 μg/kg per minute, respectively, intraosseously or intravenously."

Prevalence of Birth Defects Among Low-Birth-Weight Infants

A Population Study

Fatima Mili, MD, MPH; Larry D. Edmonds, MSPH; Muin J. Khoury, MD, PhD; Anne B. McClearn

• Major birth defects are diagnosed in about 3% to 4% of infants during their first year of life. Because many infants with birth defects have intrauterine growth retardation, are born prematurely, or both, the rate of birth defects undoubtedly varies according to the infant's birth weight. Nevertheless, the magnitude of such variation has not, to our knowledge, been adequately studied in well-defined populations. We analyzed data from the population-based Metropolitan Atlanta (Ga) Congenital Defects Program for 1978 through 1988. These data included information on 11 398 infants who were diagnosed with serious birth defects among 317 499 singleton live-born infants. Although the overall rate of birth defects was 3.6%, we observed a striking inverse relationship between the birth defects rate and the infants' birth weights. The birth defect rates were 16.2% for newborns weighing less than 1500 g at birth, 13.2% for newborns weighing from 1500 g to 1999 g, 6.2% for newborns weighing from 2000 g to 2499 g, 3.2% for newborns weighing from 2500 g to 3999 g, and 2.8% for newborns weighing 4000 g or more. Analyses by type of defect indicated that most birth defects were significantly associated with low birth weight. The higher risk of birth defects among low-birth-weight infants demonstrates that birth defects contribute to excess morbidity among low-birth-weight infants. Because of the overlap between birth defects and low birth weight, the prevention of low birth weight in the population depends greatly on a better recognition of the complex etiology of low birth weight and, in part, on the delineation of risk factors that influence the occurrence of birth defects.

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About 3% to 4% of infants are diagnosed with a major birth defect in their first year of life.[1] Because many infants with birth defects are born prematurely,[2] have intrauterine growth retardation,[3,4] or both, the rate of birth defects varies by birth weight. In a population-based study, Khoury et al[4] found a statistically significant higher risk of intrauterine growth retardation (birth weight below the race- and sex-specific 10th percentile limits for gestational age) among infants with serious birth defects (relative risk, 2.6). In population-based studies conducted in the United Kingdom,[5,6] 10% to 20% of stillborn and live-born infants weighing less than 2000 g at birth had birth defects. Investigators who obtained their information from hospital or vital records reported a high frequency of birth defects among infants with low or very low birth weight (<2500 g and <1500 g, respectively).[7-9] Case reports of infants with low and very low birth weight and specific birth defects have been frequently described in the literature: limb reduction,[10] esophageal atresia,[11-14] cleft lip and/or palate,[15,16] choanal atresia,[17] congenital heart disease,[18,19] neural tube defects[20-25] (particularly spina bifida[20,21] and anencephaly[22,23]), chromosomal disorders (including Down syndrome),[26-30] and various other syndromes.[31-39]

In this study, we present data on the rate of serious birth defects in the first year of life among low-birth-weight infants, using a population-based birth defects registry. The higher prevalence of birth defects among low-birth-weight infants has important implications for clinical care, etiologic research, and public health practice.

SUBJECTS AND METHODS

Study Population

The Metropolitan Atlanta Congenital Defects Program (MACDP) is an active surveillance system sponsored by the Centers for Disease Control, Emory University School of Medicine, and the Georgia Mental Health Institute (all located in Atlanta, Ga). Day-to-day program operations are the responsibility of the Centers for Disease Control. Created in October 1967, this program is designed to systematically collect data on all infants whose mothers reside in one of five counties in the metropolitan Atlanta area: Clayton, Cobb, DeKalb, Fulton, and Gwinnett. Subjects include live-born and stillborn infants (gestational age of at least 20 weeks or birth weight of 500 g or more) with major or serious structural defects diagnosed in the first year of life. Birth defects identified by prenatal diagnoses are excluded. Birth defects of interest include those that affect the child's survival, require substantial medical care, or cause marked physical or psychological handicap. Cases are ascertained from several sources: maternal and infant hospital medical records (20 hospi-

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From the Birth Defects and Genetic Diseases Branch, Division of Birth Defects and Developmental Disabilities, Center for Environmental Health and Injury Control, Centers for Disease Control, Public Health Service, US Department of Health and Human Services, Atlanta, Ga.

Reprint requests to the Center for Environmental Health and Injury Control, Mail Stop F-29, Centers for Disease Control, 1600 Clifton Rd NE, Atlanta, GA 30333 (Mr Edmonds).

Table 1.—Rates of Major Birth Defects in Single Live Births by Birth Weight and Race From the Metropolitan Atlanta Congenital Defects Program, 1978-1988*

Birth Weight, g	Race	No. of Infants With Birth Defects	No. of Live Births	Rate of Major Birth Defects per 100 Live Births, %	Rate Ratio (95% Confidence Interval)
≤1499	White	277	1617	17.1	5.8 (5.2, 6.5)
	Other	429	2745	15.6	4.4 (4.0, 4.9)
	Total	**706**	**4362**	16.2	5.1 (4.8, 5.5)
1500-1999	White	280	1806	15.5	5.3 (4.7, 5.9)
	Other	297	2564	11.6	3.3 (2.9, 3.7)
	Total	**577**	**4370**	13.2	4.2 (3.8, 4.5)
2000-2499	White	438	6181	7.1	2.4 (2.2, 2.6)
	Other	446	8050	5.5	1.6 (1.4, 1.7)
	Total	**884**	**14 231**	6.2	2.0 (1.8, 2.1)
2500-3999	White	4723	160 236	2.9	1.0 (reference)
	Other	3622	102 630	3.5	1.0 (reference)
	Total	**8345**	**262 866**	3.2	1.0 (reference)
≥4000	White	674	24 780	2.7	0.9 (0.9, 1.0)
	Other	212	6890	3.1	0.9 (0.8, 1.0)
	Total	**886**	**31 670**	2.8	0.9 (0.8, 0.9)

*Birth defects considered secondary to prematurity are excluded among infants born weighing less than 2500 g (eg, patent ductus arterious, patent foramen ovale, pulmonary hypoplasia, hydrocephalus associated with intraventricular hemorrhage, and undescended testicles).

tals), local cytogenetic laboratories, specialty and genetic counseling clinics, and vital records. The surveillance system has been described in detail elsewhere.[40]

The MACDP is designed to collect data on major birth defects according to the six-digit Code for Reportable Congenital Anomalies, a modification of the British Pediatric Association Code, which itself is a modification of the ninth revision of the *International Classification of Diseases*. Since 1967, trained abstractors have collected data using standardized forms. These data include identification, demographic, clinical, and diagnostic information on the infant, as well as information on the mother's prior illnesses and pregnancy history. We excluded in our analyses the following defects for infants weighing less than 2500 g at birth because they were considered secondary to prematurity: patent ductus arteriosus, patent foramen ovale, pulmonary hypoplasia, hydrocephalus associated with intraventricular hemorrhage, and undescended testicles. The analysis was restricted to live-born singleton infants. We did not use data collected before 1978 because birth weight information was not complete among live-born infants. Between January 1, 1978, and December 31, 1988, MACDP monitored 317 499 neonates born live to mothers who reside in the metropolitan Atlanta area. Of these infants, 194 620 (61.3%) were white, and 122 879 (38.7%) were of other races. Among these infants, 11 398 (3.6%) singleton infants had serious birth defects.

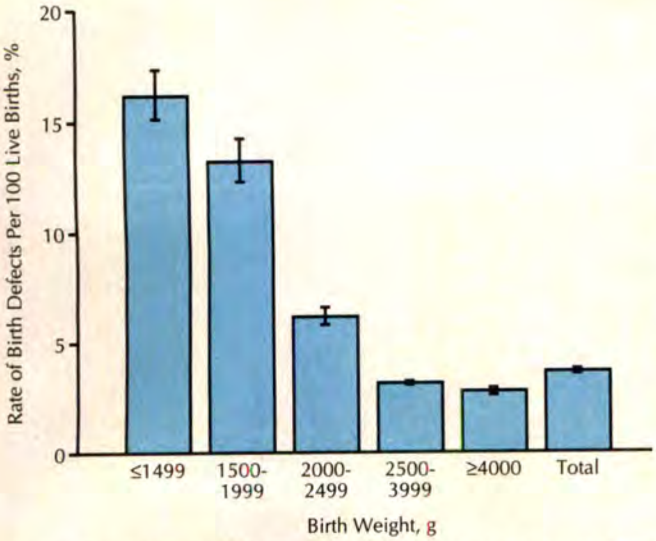
Statistical Analysis

To determine the rate of birth defects in the first year of life among live-born singleton infants in five birth-weight categories (≤1499 g, 1500 g to 1999 g, 2000 g to 2499 g, 2500 g to 3999 g, and ≥4000 g), we analyzed data from the MACDP from 1978 through 1988 using Statistical Analysis Systems software.[41] The analyses were stratified according to race, maternal age (≤35 and >35 years), sex, and birth period (1978 to 1981, 1982 to 1985, and 1986 to 1988) as well as total number of defects and 37 specific types of defects. We determined birth defect rates by dividing the number of singleton live-born infants registered in the MACDP by the total number of singleton live births in five counties of the metropolitan Atlanta area during the same period. We calculated rate ratios by dividing the rate of birth defects for infants in each birth-weight category by that of infants weighing 2500 g to 3999 g, as well as the 95% confidence interval (CI) and corresponding two-tailed *P* value. To determine the significant interactions with demographic variables, we used the Breslow-Day test.[42,43] A significant test result suggests that the association between birth weight and birth defect varied across levels of the stratification variable. In the presence of interaction, we presented race-specific estimates for each category of the covariate. In the absence of interaction, we presented adjusted Mantel-Haenszel race-specific rate ratios.

RESULTS

Table 1 shows the rates of major birth defects among live-born singleton infants in different birth-weight categories according to race and the race-specific rate ratios adjusted for different demographic variables. The Figure summarizes the rates of birth defects by birth weight. Overall, 3.6% of the singleton infants born in Atlanta from 1978 through 1988 had major birth defects diagnosed in their first year of life. Low-birth-weight infants were at a 1.76-times higher risk of having birth defects than those weighing 2500 g to 3999 g (95% confidence interval, 1.7, 1.8). Infants weighing 4000 g or more were at a slightly lower risk of having birth defects than those weighing 2,500 g to 3,999 g. Stratified analyses by maternal age, birth period, and sex did not alter measures of rate ratio between birth weight and birth defects. Nevertheless, the magnitude of the rate ratio varied substantially across the different birth period categories among infants of other races weighing 1499 g or less or 2000 g to 2499 g, and between white male and white female infants weighing 4000 g or more.

As shown in Table 2, analyses by type of defect indicated that, with some exceptions, most specific birth defects were significantly associated with low birth weight. Incidences of the following birth defects were not statistically significantly increased among certain categories of low-birth-weight infants: choanal atresia, hypoplastic left heart, endocardial cushion defects, coarctation of aorta, esophageal atresia, bladder exstrophy, and Down syndrome in infants weighing 1499 g or less; transposition of great vessels in infants weighing 1499 g or less and 1500 g to 1999 g; common truncus in infants weighing 1500 g to 1999 g and 2000 g to 2499 g; pyloric stenosis and Hirschsprung's disease in infants weighing 1499 g or less, 1500 g to 1999 g, and 2000 g to 2499 g; and, finally, cataract in infants weighing 2000 g to 2499 g. In



Rates of major birth defects in single live births by birth weight in Atlanta, Ga, from 1978 through 1988. Lines at tops of bars represent the 95% confidence interval around the rate.

addition, ventricular septal defect, endocardial cushion defects, reduction defects of limbs, Down syndrome, and congenital hip dislocation were the only defects significantly associated with the highest birth weight class. Their rate ratio was less than 1.0, except that congenital hip dislocation had a rate ratio of more than 1.0.

COMMENT

We have shown that although the overall rate of serious birth defects in these infants' first year of life is 3% to 4%, the rate of birth defects varies greatly across the different birth weight categories. From 16% to 17% of infants weighing less than 1500 g at birth had serious birth defects compared with about 3% of infants weighing 2500 g or more at birth.

A strength of our study is that Atlanta has operated a population-based birth defects registry since 1967. As an active surveillance system, MACDP maintains effective monitoring of all birth defects in infants regardless of their weight groups. In addition, the system includes multiple sources of ascertainment of serious birth defects in metropolitan Atlanta. Nevertheless, several potential limitations of this study should be considered. First, because data on gestational age have not been collected consistently among live-born infants in Atlanta, we could not directly evaluate rates of birth defects according to birth weight and gestational age. Second, our analyses are limited to live-born infants only, since stillborn infants are excluded from the denominator file (title containing the number of resident live births in the metropolitan Atlanta area). The rate of birth defects in stillborn infants may even be higher than that among live-born infants.[44] Third, some defects could more likely be detected in low-birth-weight infants (eg, cardiac defects) since sick infants tend to stay longer in the hospital. However, this type of detection bias is unlikely for severe and obvious birth defects such as neural tube defects, oral clefts, and diaphragmatic hernia. Finally, as shown in Table 1, infants of other races had lower rates of birth defects than white infants in the lower weight categories, which might reflect an underascertainment of birth defects among infants of other races.

These findings clearly suggest that low birth weight and birth defects are overlapping adverse perinatal outcomes that may share common pathogenic mechanisms. Two mechanisms may explain the association between low birth weight and birth defects: (1) birth defects can predispose infants to low birth weight if they lead to intrauterine growth retardation, preterm delivery, or both; and (2) low birth weight and birth defects may coexist because of common underlying factors.

The first mechanism suggests that the presence of birth defects is a risk factor for intrauterine growth retardation or preterm delivery. Serious birth defects are among a myriad of risk factors that contribute to intrauterine growth retardation or premature birth.[2,3,45] For example, infants with congenital heart malformations are at a higher risk of intrauterine growth retardation than those with or without other malformations.[18,19] Some researchers have suggested that hemodynamic factors, such as low oxygen saturation or perfusion, may contribute to the etiology of intrauterine growth retardation during fetal development and may be associated with some heart defects causing hypotrophy of organs such as the spleen, liver, kidneys, adrenals, and pancreas.[46] Analyses of the MACDP data[4] indicated that of 13 074 infants born with major birth defects in Atlanta between 1970 and 1984, 22.3% had intrauterine growth retardation (relative risk, 2.6; 95% CI, 2.5, 2.7); and of 48 defect categories evaluated in the analyses, 46 were associated with intrauterine growth retardation. The findings were particularly striking in infants with chromosomal anomalies (83.7% for infants with trisomy 18 syndrome; relative risk, 46) and anencephaly (73.3%; relative risk, 25). Furthermore, infants with multiple malformations were at a higher risk of having intrauterine growth retardation than those with isolated malformations. The risk increased substantially as the number of defects increased.

Likewise, birth defects could also be an important factor of premature birth. Fetal congenital malformations that seem to be associated with premature birth include anencephaly associated with polyhydramnios, renal agenesis associated with oligohydramnios, multiple congenital anomalies, and central nervous system anomalies.[2] Analyses of the MACDP showed that 21.3% of infants with birth defects are born prematurely (less than 37 weeks of gestation) compared with 5.6% of a random sample of all Atlanta infants (M.J.K. and A.B.M., Centers for Disease Control, unpublished data, 1990).

The second mechanism suggests that common factors may underlie the pathogenesis of low birth weight and birth defects. Some evidence indicates that embryologic and fetal growth are regulated by interactions between genes, environmental and nutritional components, fetal and placental hormones, and growth factors.[47,48] For example, birth weight correlates with fetal plasma levels of insulinlike growth factor I, although both insulinlike growth factors I and II increase gradually during fetal development up to birth.[47] Moreover, in teratogenesis, mechanisms that may be involved in the development of abnormal tissue include gene or chromosomal mutations, alteration of intercellular communication or membrane properties, and modulation of hormone receptors.[49] A well-established environmental risk factor for both birth defects and low birth weight is maternal consumption of alcohol during pregnancy.[50,51] Analyses of data from the MACDP, the Emory genetic clinics, and the Georgia Mental Health Institute showed that of 110 infants with

Table 2.—Rate of Specific Birth Defects in Single Live Births by Birth Weight Category From the Metropolitan Atlanta Congenital Defects Program, 1978-1988*

		Birth Weight, g									
		≤1499		1500-1999		2000-2499		2400-3999		≥4000	
Defect	**No. of Cases**	**Rate per 1000 Live Births, %**	**Rate Ratio**	**Rate per 1000 Live Births, %**	**Rate Ratio**	**Rate per 1000 Live Births, %**	**Rate Ratio**	**Rate per 1000 Live Births, %**	**Rate Ratio**	**Rate per 1000 Live Births, %**	**Rate Ratio**
Anencephaly	63	5.5	111.3	3.4	69.4	0.6	12.8	0.05	1.0	0.06	1.3†
Spina bifida	189	2.3	4.6	1.8	3.7	1.3	2.5	0.5	1.0	0.7	1.4†
Encephalocele	56	1.8	13.8	1.1	8.6	0.4	2.6	0.1	1.0	0.09	0.7†
Hydrocephalus	236	12.6	28.3	5.0	11.3	1.8	4.1	0.5	1.0	0.5	1.1†
Microcephalus	187	8.0	26.0	6.2	20.1	2.5	8.2	0.3	1.0	0.3	0.8†
Cataract	74	1.6	8.0	0.7	3.4	0.4	1.7†	0.2	1.0	0.2	0.9†
Anophthalnia and microphthalmia	116	3.7	16.1	3.4	15.0	1.5	6.5	0.2	1.0	0.1	0.6†
With or without cleft lip palate	310	3.9	4.7	5.0	6.1	1.7	2.0	0.8	1.0	0.9	1.1†
Cleft palate	155	3.0	7.5	3.2	8.1	1.2	3.0	0.4	1.0	0.2	0.6†
Choanal atresia	34	0.2	2.9†	0.5	5.7	0.5	6.2	0.08	1.0	0.09	1.2†
Ventricular septal defect	695	10.6	5.7	9.4	5.1	5.8	3.1	1.8	1.0	1.3	0.8
Tetralogy of Fallot	110	0.9	3.3	1.8	6.5	1.1	3.7	0.3	1.0	0.3	1.0†
Transposition of great vessels	148	0.7	1.6†	0.9	2.1†	0.8	1.9	0.4	1.0	0.4	1.0†
Hypoplastic left heart	102	0.7	2.5†	1.6	5.9	0.7	2.6	0.3	1.0	0.4	1.3†
Common truncus	24	0.5	6.7	0.2	3.3†	0.2	3.1†	0.07	1.0	0.0	0.0
Endocardial cushion defects	108	0.2	0.7†	1.1	3.7	1.2	3.8	0.3	1.0	0.09	0.3
Coarctation of aorta	122	0.5	1.3†	1.4	3.8	0.7	2.0	0.4	1.0	0.3	0.9†
Esophageal atresia	69	0.5	3.5†	4.1	31.8	1.0	7.6	0.1	1.0	0.03	0.2†
Small intestinal atresia	55	2.3	25.1	2.1	22.6	0.8	8.5	0.09	1.0	0.03	0.3†
Anorectal atresia	111	2.5	11.0	2.8	12.0	1.4	6.2	0.2	1.0	0.3	1.1†
Pyloric stenosis	445	0.7	0.5†	0.9	0.7	1.1	0.8†	1.4	1.0	1.6	1.2†
Hirschsprung's disease	51	0.0	0.0	0.0	0.0	0.1	0.8†	0.2	1.0	0.2	0.9†
Diaphragmatic hernia	64	0.7	3.9	0.7	3.9	0.4	2.4	0.2	1.0	0.2	1.0†
Omphalocele	73	0.7	4.3	2.3	14.3	0.8	4.8	0.2	1.0	0.2	1.4†
Gastroschisis	60	1.6	16.2	2.5	25.4	1.1	10.7	0.1	1.0	0.03	0.3†
Renal agenesis	87	3.4	33.5	5.0	49.0	1.3	13.0	0.1	1.0	0.1	1.2†
Cystic kidneys	96	1.2	5.6	3.0	14.5	1.4	6.8	0.2	1.0	0.1	0.6†
Bladder exstrophy	6	0.0	0.0	0.2	12.0	0.0	0.0	0.02	1.0	0.0	0.0
Hypospadias	919	8.5	3.3	8.5	3.3	5.6	2.2	2.6	1.0	2.6	1.0†
Anomalies of renal pelvis and ureter	187	3.7	8.2	2.8	6.2	1.8	3.9	0.5	1.0	0.5	1.2†
Clubfoot	858	9.4	3.8	8.9	3.6	4.6	1.8	2.5	1.0	2.0	0.8†
Reduction defects of limbs	136	2.5	8.0	3.7	11.7	1.7	5.4	0.3	1.0	0.09	0.3
Polydactyly	732	5.0	2.3	6.4	3.0	3.8	1.8	2.2	1.0	2.0	0.9†
Congenital hip dislocation	220	1.6	2.7	1.8	3.1	1.4	2.4	0.6	1.0	0.9	1.5
Down syndrome	300	1.4	1.6†	2.1	2.4	3.4	4.0	0.9	1.0	0.4	0.5
Trisomy 13	27	0.5	8.6	0.9	17.2	0.4	7.9	0.05	1.0	0.03	0.6†
Trisomy 18	46	2.8	120.5	3.4	150.4	0.9	40.0	0.02	1.0	0.0	0.0

*Birth defects considered secondary to prematurity are excluded among infants weighing less than 2500 g (eg, patent ductus arteriosus, patent foramen ovale, pulmonary hypoplasia, hydrocephalus associated with intraventricular hemorrhage, and undescended testicles).
†Not statistically significant.

fetal alcohol syndrome or fetal alcohol effect (diagnosed according to a scoring scheme developed by the Georgia Mental Health Institute), about 84% have low birth weight (M. L. Martin, and A.B.M., Centers for Disease Control, unpublished data, 1990). In addition, of 550 live-born cases reported in the literature worldwide,[52] 77% had low birth weight.

Finally, these findings have implications for clinical care, surveillance, and prevention. First, birth defects contribute to increased morbidity and mortality among low-birth-weight infants and are often associated with costly medical and surgical care that compounds medical problems related to low birth weight. These data are consistent with a recent analysis of National Center for Health Statistics data for the 1983 US birth cohort, indicating that the contribution of birth defects to infant mortality is relatively high among infants born weighing less than 2500 g.[53] The proportional mortality due to birth defects was 30% to 50% among those weighing 1500 g to 2499 g, compared with 20% to 30% among those weighing 2500 g or more.

Second, an increasing number of statewide programs are conducting or planning birth defect surveillance activities. Because low-birth-weight infants are at high risk for birth defects, targeting medical records of low-birth-weight infants should improve the overall ascertainment of birth defects in the population. Lastly, because a substantial proportion of low-birth-weight infants have associated birth defects, public health prevention strategies should include the complex etiology and pathogenesis of low birth weight and attempt to better delineate and prevent risk factors that influence the occurrence of birth defects.

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Gerald S. Berenson, MD
(*Arch Intern Med.* 1991;151:2017-2022)

Substantial Improvement in Compliance With Universal Precautions in an Emergency Department Following Institution of Policy

Gabor D. Kelen, MD; Gary B. Green, MD; David A. Hexter, MD;
Dewitt C. Fortenberry, MD; Eric Taylor, MD;
Deborah H. Fleetwood, RN; Keith T. Sivertson, MD
(*Arch Intern Med.* 1991;151:2051-2056)

Sudden Deaths and Apparent Life-Threatening Events in Hospitalized Neonates Presumed to Be Healthy

David J. Burchfield, MD, D. Jim Rawlings, MD

• We describe 10 apparently healthy newborns who were patients in a level 1 nursery and were found by caregivers to be limp, apneic, and requiring resuscitation. All patients were between ages 15 hours and 3½ days, products of term gestations, and of appropriate weight for gestational age. Prenatal or perinatal complications were present in nine of the 10 patients; in no patient was the complication considered a risk for serious, late-onset neonatal problems. All patients had been examined by a physician and were deemed to be in good health before the apparent life-threatening event. Subsequent to the event, each patient required positive pressure ventilation and seven patients received chest compressions. Five patients died. Autopsies were performed on four of the five patients and in none was an adequate explanation for death established. Intrathoracic petechiae were found in one patient whose sibling had died of sudden infant death syndrome at age 11 weeks. Evaluation of the five survivors failed to determine a cause for the episodes. Of the five survivors, one had normal results of developmental examination at age 6 months, while the remaining four survivors had severe neurologic impairment at age 1 year. Apparent life-threatening events occur in hospitalized newborns presumed to be normal and may be a manifestation of early sudden infant death syndrome or early near-miss sudden infant death syndrome.

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Sudden infant death syndrome (SIDS) is recognized as the largest single cause of postneonatal infant mortality, with a peak incidence between ages 2 and 4 months, followed by a rapid decline in frequency by age 6 months.[1-3] When studied, 1% to 3% of cases of SIDS were found to occur during the first 2 weeks of life.[3-5] Many investigators excluded this age group from their epidemiologic studies[6-14] because of possible undetected perinatal events that may have led to the death. A diagnosis of SIDS during the first 2 postnatal weeks is often regarded with suspicion because of either the low incidence or the lack of inclusion in epidemiologic studies.

Between October 1985 and April 1990, 10 newborns were cared for in our neonatal intensive care units who were less than age 3½ days and had been found "limp and lifeless" or apneic by their caregivers in a level 1 newborn nursery. All the patients had been examined by a physician and were considered healthy. In our judgment, these events are best ascribed to SIDS or apparent life-threatening events (ALTEs) during the early neonatal period. We describe these 10 newborns to highlight that ALTEs occasionally occur in the early newborn period.

MATERIALS AND METHODS

The Regional Perinatal Intensive Care Unit at Shands Hospital in Gainesville, Fla, is a 20-bed, level 3 nursery with a mean of 760 patients admitted annually. Approximately 40% of the patients are transferred in; most transferees live within the 16-county area that is served by hospitals with level 1 nurseries. The Citywide Neonatology Program in Jacksonville, Fla, has 40 level 3 beds with a mean of 960 patients admitted annually. Of these patients, approximately 15% are transferred, primarily from level 1 and 2 nurseries within Jacksonville and five surrounding counties. Each patient in this report was either born at one of the level 3 hospitals and was initially cared for in the normal newborn nursery or was transferred to the level 3 hospital from a referring hospital following an acute event. All prenatal and perinatal data were obtained retrospectively from the patients' and their mothers' hospital records. In addition, all survivors were examined at age 6 months, and four of the five survivors were again examined at age 12 months in the State of Florida prospective longitudinal follow-up program of high-risk neonates.

PATIENT REPORT

A 4.03-kg white male neonate was born at 40 weeks' gestation to a healthy 19-year-old primigravida who had had frequent prenatal care. She smoked approximately 10 cigarettes each day and had mild pre-eclampsia treated with bedrest. She went into spontaneous labor 36 hours before delivery, with spontaneous rupture of the amniotic membranes 20 hours before delivery. She received meperidine hydrochloride (25 mg) and promethazine hydrochloride (10 mg) 5 hours before delivery. The mother received general anesthesia for a cesarean section due to cephalopelvic disproportion. The newborn received an Apgar score of 8/9 at 1 and 5 minutes. Resuscitation included nasopharyngeal suctioning for light meconium-stained fluid. Physical examination of the newborn revealed a weight in the 95th percentile. Results of the remainder of the examination were normal. The newborn had blood glucose values (Chemstrip bG, Boehringer Mannheim Corp, Indianapolis, Ind) of 2.2 mmol/L at ages 0.5, 2, and 4 hours. The newborn received formula by mouth begin-

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From the Department of Pediatrics, Division of Neonatology, University of Florida College of Medicine, Gainesville (Dr Burchfield) and Jacksonville (Dr Rawlings).

Reprint requests to Department of Pediatrics, Division of Neonatology, University of Florida College of Medicine, PO Box 100296, Gainesville, FL 32610-0296 (Dr Burchfield).

Table 1.—Maternal and Perinatal Data*

Patient No.	Maternal Age, y	Race	Gravity	Parity (F-P-A-L)	Syphilis Serology	Health, Pregnancy, L & D Complications	Type of Delivery
1	21	B	8	3-0-4-3	Nonreactive	Previous sudden infant death syndrome at 11 wk; fluid leak 4-6 wk; foul smell at delivery; nuchal cord	Spontaneous vaginal delivery
2	22	W	2	0-0-1-0	Nonreactive	Thick meconium in fluid; cords clear to inspection; 10% abruption	Spontaneous vaginal delivery, w/vacuum
3	27	W	2	0-0-1-0	Nonreactive	Elective abortion at 8 wk; glucosuria, normal glucose tolerance test result; light meconium	Spontaneous vaginal delivery w/vacuum
4	28	B	1	0-0-0-0	Reactive	Mild essential hypertension; pre-eclampsia	Cesarean section
5	32	W	1	0-0-0-0	Nonreactive	Thin meconium; failure to progress	Cesarean section
6	17	W	1	0-0-0-0	. . .	15% abruption	Spontaneous vaginal delivery
7	18	W	1	0-0-0-0	. . .	Smoked 1 pack of cigarettes per day; marijuana use	Spontaneous vaginal delivery, low
8	19	W	1	0-0-0-0	Nonreactive	Smoked ½ pack of cigarettes per day; mild pre-eclampsia	Cesarean section
9	21	W	2	1-0-0-1	Nonreactive	Normal	Spontaneous vaginal delivery
10	19	W	1	0-0-0-0	. . .	Decreased fetal movement near term; glucosuria, normal glucose tolerance test result	Spontaneous vaginal delivery, low forceps

*F-P-A-L indicates full term, premature, abortions, living; L & D, labor and delivery.

ning at age 6 hours and was fed 30 mL to 60 mL per feeding. The newborn was examined at age 14 hours by a pediatrician and was considered healthy. He nursed well from a bottle throughout the first 32 hours of life. At age 36 hours, routine nursing care was documented. About 10 minutes later, a nurse found the newborn in the bassinet limp, cyanotic, and without a detectable heart rate. She immediately administered assisted ventilation with bag and mask, and began chest compressions. The newborn's trachea was intubated and the heart rate returned to greater than 100 beats per minute within 2 minutes. However, spontaneous respiration did not return for 45 minutes. Plasma electrolyte levels were within normal limits and plasma glucose was 13.5 mmol/L following resuscitation. No abnormalities were found on a chest film. Blood was obtained for aerobic and anaerobic culture and the newborn was transferred to the Regional Perinatal Intensive Care Unit at Shands Hospital. The patient had a seizure during the transfer and was administered phenobarbital (40 mg/kg) intravenously. Further treatment included fluid restriction, hyperventilation, antibiotics, and nitroprusside for severe hypertension with lactic acidosis. Computed tomography of the brain performed within 12 hours of the event revealed no structural abnormalities or abnormal collections of blood. Blood cultures obtained after the event were sterile. Results of serum amino acid profile were within normal limits. Other than irregular respiratory efforts, the newborn had no evidence of brain-stem function for 7 days and artificial ventilation was withdrawn. Autopsy revealed hypoxic-ischemic damage to the brain, but no developmental defects were noted.

RESULTS

Table 1 summarizes maternal and perinatal data for each of the 10 patients who experienced ALTEs. Ellipses indicate that no information was available for that category. Nine of the 10 pregnancies had some complicating factor prenatally or ante partum but in no case was the complication considered a risk for serious, late-onset neonatal problems. Reactive serologic results occurred in one mother who received treatment for syphilis 1 year previously. No evidence of syphilis in the newborn was evident at autopsy.

Table 2 summarizes postnatal data for each case. Ellipses indicate that documentation was too vague to obtain specific times. All newborns were examined by a pediatrician or family practitioner before the ALTE and were considered healthy. The "Last Fed" and "Last Seen" columns in Table 2 record the times that the staff interacted with the patients. All patients had sucked formula or breast milk within 6 hours of the event except patient 8, who drank glucose water 3 times before the event. The patients' ages at the time of the ALTE ranged from 15.3 to 76.5 hours. Six of the ALTEs took place between 3 AM and 6 AM. The rest were interspersed throughout the day.

All newborns required assisted ventilation and seven of the 10 required chest compressions. Autopsies were performed on four of the five who died. Patient 1, whose sibling had died of SIDS, had thymic and pulmonary petechiae. The other autopsies revealed no abnormalities. Patient 6 died at age 21.7 hours and had a postmortem blood culture that yielded coagulase-negative *Staphylococcus*. He had a normal white blood cell count and differential count, normal cerebrospinal fluid study results, no growth on his urine culture, and no evidence of focal infection at autopsy. These facts suggest that this bacterium was not an overwhelming pathogen in the newborn. Coagulase-negative *Staphylococcus* has been a common contaminant in that particular nursery and has been identified as a pathogen only infrequently, usually in chronically stressed premature infants with in-dwelling central catheters.

Immediate postevent arterial blood gas measurements were available for nine of the 10 patients (Table 2). Metabolic acidosis of moderate to severe degree was uniformly present. The $PACO_2$ and PAO_2 values varied, perhaps in part due to the amount of ventilation and oxygenation provided during initial resuscitation.

Table 2.—Postnatal Data

					Time, min*			Arterial Blood Gas				
Patient No.	Sex	Apgar at 1 min/5 min	Gestational Age, wk	Weight, g	Last Fed	Last Seen	Postnatal Age, h	pH	PCO_2	PO_2	BE†	Outcome
1	F	3/8	40	3465	–175	–175	17.5	6.82	40	90	–29	Died; autopsy revealed thymic and pulmonary petechiae; focal choroid plexus hemorrhage
2	F	8/9	39	3125	. . .	–15	76.5	6.95	23	317	–27	Died; organ donor; no autopsy; removed from ventilator
3	F	9/9	39	3490	–175	–15	15.3	6.74	38	309	–32	Lived; normal evaluation at age 6 mo.
4	M	9/10	40	3949	. . .	–75	69.0	6.95	126	46	–13	Died; autopsy revealed normal findings
5	M	9/10	39	3900	–60	–60	17.3	6.88	18	474	–22	Lived; severe neurologic impairment
6	M	8/9	41	3550	–347	–37	21.7	. . .	. . .	. . .	. . .	Died; autopsy revealed normal findings
7	F	8/10	40	3025	–126	–126	27.3	7.04	20	443	–24	Lived; severe neurologic impairment
8	M	8/9	40	4028	–285	–10	36.5	6.97	23	641	–27	Died; autopsy revealed normal findings
9	M	9/9	39	3550	–240	–10	36.5	7.27	22	372	–10.6	Lived; severe neurologic impairment
10	M	8/9	39	3200	–259	–19	36.7	6.85	65	80	–20.1	Lived; severe neurologic impairment

*Last Fed and Last Seen show time before apparent life-threatening event.
†BE indicates base excess and is expressed in milliequivalent per liter.

Survivors had extensive but unrevealing diagnostic evaluations that included sterile blood cultures, normal cranial computed tomograms, normal serum electrolyte levels, normal electrocardiograms, no reducing substance in the urine, and normal amino acid profile in either serum or urine or both. Of the five survivors, four were severely neurologically impaired at age 1 year. At age 6 months, patient 3 scored within normal ranges on all aspects of the Bayley Scales of Infant Development. This patient's family moved out of state, so the patient could not be evaluated at age 1 year.

COMMENT

We describe 10 newborns who suffered an ALTE during the early newborn period. We believe that these newborns demonstrated no signs or symptoms of ill health and that their admission to and care provided in a level 1 or "normal newborn" nursery was warranted. Postresuscitation and/or autopsy studies did not identify causes for the events.

Because the 10 neonates were born in five different cities and because we cannot be certain that no similar cases occurred in these cities, the incidence of early neonatal ALTEs cannot be defined. Polberger and Svenningsen[15] described 13 neonates who suffered either early SIDS or early near-miss SIDS. Ten of these newborns were born at the authors' institution, which allowed them to establish an incidence of early SIDS or early near-miss SIDS in their hospital of 0.50 per 1000 full-term infant births. Four of the 13 neonates were later proven to have bacterial sepsis and two had anemia. However, seven of the neonates had no identifiable cause for their life-threatening or life-taking episodes.

Six of the 10 patients described herein experienced their ALTE in the early morning. In the study by Polberger and Svenningsen, all 13 neonates experienced their ALTE between 11 PM and 6 AM. These findings are consistent with the epidemiology of SIDS occurring in the early morning.[4,16]

The characteristic SIDS event is quiet, sudden, unexpected, and life-threatening. Autopsy reveals no anatomic cause for the demise, and may show mild pulmonary congestion, inflammation, or intrathoracic petechiae.[3,16] Since nine of the 10 patients in this study were in nurseries and under professional care at the time they experienced an ALTE, the circumstances surrounding these events are well documented. The patients fit into the diagnostic category of SIDS or ALTE, despite their early postnatal age. Because the frequency of SIDS is known to be quite low during the first 2 weeks of extrauterine life, the closer to birth that such an event occurs, the greater is the tendency to view a diagnosis of SIDS with suspicion. When faced with a patient who presents with an ALTE during the first hours or days of life, the physician should diligently seek known causes of severe apnea and bradycardia, especially treatable ones. If death occurs, a complete postmortem examination should be performed. If no cause of death is found, it is important to classify the event as SIDS and not to rule out this diagnosis based on the age of the patient. Pediatric caregivers who might be involved with similar cases should know that neonates may have an unexplained ALTE in the early newborn period.

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In Other AMA Journals

ARCHIVES OF OPHTHALMOLOGY

Pigmented Paravenous Retinochoroidal Atrophy: Discordant Expression in Monozygotic Twins

Kent W. Small, MD, W. Banks Anderson, Jr, MD
(*Arch Ophthalmol.* 1991;109:1408-1410)

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CHILDREN'S ADVIL® SUSPENSION is indicated for the relief of primary dysmenorrhea.

CONTRAINDICATIONS: Patients hypersensitive to ibuprofen or patients with all or part of the syndrome of nasal polyps, angioedema, and bronchospastic reactivity to aspirin or other nonsteroidal anti-inflammatory agents. Anaphylactoid reactions to ibuprofen have occurred in such patients.

WARNINGS: Risk of GI Ulcerations, Bleeding, and Perforation with NSAID Therapy: Physicians should remain alert for ulceration and bleeding in patients treated chronically with NSAIDS even in the absence of previous GI tract symptoms. In patients observed in clinical trials of several months' to two years' duration, symptomatic upper GI ulcers, gross bleeding or perforation appear to occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for one year.

Except for a prior history of serious GI events and other risk factors known to be associated with peptic ulcer disease, no risk factors have been associated with increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less well than other individuals and most spontaneous reports of fatal GI events are in this population.

PRECAUTIONS: General: Because serious GI tract ulceration and bleeding can occur without warning symptoms, physicians should follow chronically treated patients for the signs and symptoms of ulceration and bleeding.

Blurred and/or diminished vision, scotomata, and/or changes in color vision have been reported. If a patient develops such complaints the drug should be discontinued and the patient should have an ophthalmologic examination.

Fluid retention and edema have been reported with ibuprofen; therefore, the drug should be used with caution in patients with a history of cardiac decompensation or hypertension.

Ibuprofen can inhibit platelet aggregation and prolong bleeding time. CHILDREN'S ADVIL® SUSPENSION should be used with caution in persons with intrinsic coagulation defects and those on anticoagulant therapy.

The antipyretic and anti-inflammatory activity of ibuprofen may reduce fever and inflammation, thus diminishing their utility as diagnostic signs in detecting complications of presumed noninfectious, noninflammatory painful conditions.

Small decreases (usually not exceeding one gram) in hemoglobin and hematocrit with an apparent dose response relationship have been observed following chronic administration. If there are no signs of bleeding, it is probably not clinically important.

To avoid exacerbation of disease or adrenal insufficiency, patients on prolonged corticosteroid therapy should have their therapy tapered slowly when CHILDREN'S ADVIL® SUSPENSION is added to the treatment program.

Aseptic meningitis: Aseptic meningitis with fever and coma has been observed on rare occasions in adult patients on ibuprofen therapy. Although it is more likely to occur in patients with systemic lupus erythematosus and related connective tissue diseases, it has been reported in adult patients who do not have underlying chronic disease. If signs or symptoms of meningitis develop in a patient on CHILDREN'S ADVIL® SUSPENSION, the possibility of its being related to ibuprofen should be considered.

Renal Effects: As with other nonsteroidal anti-inflammatory drugs, long-term administration of ibuprofen to animals has resulted in renal papillary necrosis and other abnormal renal pathology. In humans, there have been reports of acute interstitial nephritis with hematuria, proteinuria, and occasionally nephrotic syndrome.

A second form of renal toxicity has been seen in patients with prerenal conditions leading to reduction in renal blood flow or blood volume. In these patients, administration of a nonsteroidal anti-inflammatory drug may cause a dose dependent reduction in prostaglandin formation and precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, and those taking diuretics and the elderly. Those patients at high risk who chronically take CHILDREN'S ADVIL® SUSPENSION should have renal function monitored if they have signs or symptoms of azotemia. Discontinuation of nonsteroidal anti-inflammatory drug therapy is typically followed by recovery to the pretreatment state.

Since ibuprofen is eliminated primarily by the kidneys, patients with significantly impaired renal function should be closely monitored and a reduction in dosage should be anticipated to avoid drug accumulation.

Information for Patients: Physicians may wish to discuss with their patients the potential risks and likely benefits of treatment with CHILDREN'S ADVIL® SUSPENSION.

Laboratory Tests: Meaningful (3 times the upper limit of normal) elevations of SGPT or SGOT (AST) occurred in controlled clinical trials in less than 1% of patients. A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of more severe hepatic reactions while on therapy with ibuprofen. If abnormal liver tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur, CHILDREN'S ADVIL® SUSPENSION should be discontinued.

Diabetes: Each 5 mL of CHILDREN'S ADVIL® SUSPENSION contains 2.5 g of sucrose which should be taken into consideration when treating patients with impaired glucose tolerance. It also contains 350 mg of sorbitol per 5 mL. Although in clinical trials CHILDREN'S ADVIL® SUSPENSION was not associated with more diarrhea than control treatments, should a patient develop diarrhea, the physician may wish to review the patient's dietary intake of sorbitol from other sources.

Drug Interactions: *Coumarin-type Anticoagulants:* Bleeding has been reported when ibuprofen and other nonsteroidal anti-inflammatory agents have been administered to patients on coumarin-type anticoagulants; the physician should be cautious when administering CHILDREN'S ADVIL® SUSPENSION to patients on anticoagulants.

Aspirin: Concurrent use of aspirin is not recommended.

Methotrexate: In vitro studies indicate that ibuprofen could enhance the toxicity of methotrexate. Caution should be used if CHILDREN'S ADVIL® SUSPENSION is administered concomitantly with methotrexate.

H_2 Antagonists: In studies with human volunteers, coadministration of cimetidine or ranitidine with ibuprofen had no substantive effect on ibuprofen serum concentrations.

Furosemide: Ibuprofen can reduce the natriuretic effect of furosemide and thiazides in some patients. During concomitant therapy with CHILDREN'S ADVIL® SUSPENSION, the patient should be observed closely for signs of renal failure as well as to assure diuretic efficacy.

Lithium: Ibuprofen produced an elevation of plasma lithium levels (15%) and a reduction in renal lithium clearance (19%) in a study of 11 normal volunteers during the period of concomitant drug administration. Patients should be observed carefully for signs of lithium toxicity. Read package insert for lithium before its use.

Pregnancy: Administration of ibuprofen is not recommended during pregnancy or for use by nursing mothers.

Infants: Safety and efficacy of CHILDREN'S ADVIL® SUSPENSION in children below the age of 12 months have not been established.

ADVERSE REACTIONS: The most frequent type of adverse reaction occurring with CHILDREN'S ADVIL® SUSPENSION is gastrointestinal. In clinical trials among adults involving chronic administration of ibuprofen, the percentage of patients reporting one or more gastrointestinal complaints ranged from 4% to 16%.

Incidence Greater Than 1% (but less than 3%), Probable Causal Relationship (see PRECAUTIONS): Abdominal cramps or pain, abdominal distress, constipation, diarrhea, epigastric pain,* fullness of the GI tract (bloating and flatulence), heartburn,* indigestion, nausea,* nausea and vomiting; dizziness,* headache, nervousness; pruritus, rash* (including maculopapular type); tinnitus; decreased appetite; edema, fluid retention (generally responds promptly to drug discontinuation).

Precise Incidence Unknown (but less than 1%), Probable Causal Relationship (see PRECAUTIONS): Abnormal liver function tests, gastric or duodenal ulcer with bleeding and/or perforation, gastritis, gastrointestinal hemorrhage, hepatitis, jaundice, melena, pancreatitis; alopecia, erythema multiforme, Stevens-Johnson syndrome, urticaria, vesiculobullous eruptions; aseptic meningitis with fever and coma, confusion, depression, emotional lability, insomnia, somnolence; amblyopia (blurred and/or diminished vision, scotomata and/or changes in color vision), hearing loss; agranulocytosis, aplastic anemia, decreases in hemoglobin and hematocrit, eosinophilia, hemolytic anemia (sometimes Coombs' positive), neutropenia, thrombocytopenia with or without purpura; congestive heart failure in patients with marginal cardiac function, elevated blood pressure, palpitations; anaphylaxis, bronchospasm (see CONTRAINDICATIONS), syndrome of abdominal pain, fever, chills, nausea and vomiting; acute renal failure in patients with pre-existing significantly impaired renal function, azotemia, cystitis, decreased creatinine clearance, hematuria, polyuria; dry eyes and mouth, gingival ulcers, rhinitis.

Precise Incidence Unknown (but less than 1%), Causal Relationship Unknown: Dream abnormalities, hallucinations, paresthesias, pseudotumor cerebri; photoallergic skin reactions, toxic epidermal necrolysis; cataracts, conjunctivitis, diplopia, optic neuritis; bleeding episodes (e.g., epistaxis, menorrhagia); acidosis, gynecomastia, hypoglycemic reactions; arrhythmias (sinus tachycardia, sinus bradycardia); angioedema, Henoch-Schönlein vasculitis, lupus erythematosus syndrome, serum sickness; renal papillary necrosis.

*Reactions occurring in 3% to 9% of adult patients treated with ibuprofen.

OVERDOSAGE: Patients with a history of ingestion of greater than 100 mg/kg should have induced emesis or gastric lavage. Multiple dose oral administration of activated charcoal may be useful. Supportive therapy may include oxygen, respiratory support, and parenteral fluids. Because the drug is acidic and excreted in the urine, administration of sodium bicarbonate and induction of diuresis may be beneficial.

DOSAGE AND ADMINISTRATION: Fever: 5 mg/kg if baseline temperature is 102.5°F or below or 10 mg/kg if baseline temperature is greater than 102.5°F, every 6-8 hours (children); 400 mg every 4-6 hours (adults).

Mild to moderate pain in adults: 400 mg every 4 to 6 hours.
Juvenile Arthritis: 30-40 mg/kg day in 3 or 4 divided doses.
RA and OA: 1200-3200 mg per day in 3 or 4 divided doses.
Dysmenorrhea: 400 mg every 4 hours.

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How Much of Neonatal Encephalopathy Is due to Birth Asphyxia?

Karin B. Nelson, MD, Alan Leviton, MD

• In the literature on neonatal encephalopathy, the pervasive assumption is that once infants with major malformations or infections have been excluded, most of the remaining cases are due to birth asphyxia. Assessing the proportion of neonatal encephalopathy that is due to asphyxia during birth is difficult because of problems in defining asphyxia and neonatal encephalopathy and in recognizing the cause of neonatal neurologic illness. Available evidence indicates that neonatal neurologic signs are not strongly related to obstetric complications, signs of fetal distress, or biochemical markers usually considered to indicate perinatal asphyxia. Most studies that have sought positive evidence of independent markers of intrapartum asphyxia have found them to be absent in a large majority of neurologically symptomatic neonates. We conclude that the proportion of neonatal encephalopathy that is asphyxial in origin is not known but warrants examination, especially in view of the probable need in the near future to identify, on the basis of *evidence available in the first hour or so of life*, suitable candidates for clinical trials of powerful but risky treatments of birth asphyxia.

(*AJDC*. 1991;145:1325-1331)

Intrapartum asphyxia severe enough to produce irreversible brain injury in the term infant is regularly followed by signs of neurologic illness in the neonatal period.[1-3] Neonatal encephalopathy (NE) is a clinically defined syndrome of disturbed neurologic function in the earliest days of life in the term infant, manifested by difficulty with initiating and maintaining respiration, depression of tone and reflexes, subnormal level of consciousness, and often by seizures.[4] Other names for this syndrome, such as hypoxic-ischemic encephalopathy (HIE) and postasphyxial encephalopathy, suggest that this syndrome almost always follows recent asphyxia (or hypoxia or ischemia or some combination of these), especially during birth.

Is it true that NE is usually due to asphyxia? This question gains a fresh urgency because new treatments intended to prevent death or long-term neurologic deficits from birth asphyxia are on the horizon.[5-10] These powerful and potentially risky therapies will require an ability to identify—and identify very rapidly—infants whose problems are truly secondary to asphyxia at birth and serious enough to warrant some risk in their treatment.

In this article, we review the knowledge base currently available for assessing the fraction of NE that is due to asphyxia at birth and ask how well predictors of neonatal asphyxia that are *available within the first hour or two of life* permit us to recognize seriously asphyxiated infants who might be candidates for immediate intervention for birth asphyxia.

DEFINITIONS OF BIRTH ASPHYXIA AND THEIR USE AS PREREQUISITES TO DEFINITIONS OF NE

Asphyxia

A major initial problem in assessing the relationship between NE and asphyxia is the lack of generally accepted and operationally defined measures of hypoxia, ischemia, or asphyxia. Asphyxia has been defined as "the depletion of oxygen and the accumulation of carbon dioxide leading to acidosis."[11] What level of oxygen depletion, carbon dioxide accumulation, or acidosis warrants the term asphyxia?

Defects in oxygenation may be accompanied by hypoperfusion and lead to tissue ischemia. Levels of oxygen or carbon dioxide in the brain are not measured directly. Most investigators of asphyxia in the newborn human have employed instead a variety of the following clinical markers to suggest the presence of asphyxia: meconium in the amniotic fluid, fetal bradycardia, abnormal patterns of fetal heart rate, abnormalities on blood flow studies or neuroimaging, or biochemical markers. Towell[12] has discussed the range and variability of these markers. The different approaches of investigators who have implicated asphyxia and fetal distress adds to the confusion (Table 1).

NE

In 1976, Sarnat and Sarnat[2] described 21 depressed newborns with an encephalopathy following fetal distress, but they did not provide neurologic criteria for inclusion in the sample. Each infant had an Apgar score less than 6 at 1 or 5 minutes or "a well-defined episode of fetal

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From the Neuroepidemiology Branch, National Institute of Neurological Disorders and Stroke, Bethesda, Md (Dr Nelson), and Children's Hospital, and Harvard Medical School, Boston, Mass (Dr Leviton).

Reprint requests to 7550 Wisconsin Ave, Room 700, Bethesda, MD 20892 (Dr Nelson).

Table 1.—Intranatal or Immediate Postnatal Requirements for Diagnoses of Newborn Encephalopathy

- Neonatal encephalopathy
  - Sarnat and Sarnat,[2] 1976
    - One of two criteria
      - Well-defined episode of fetal distress (not defined)
      - Apgar score, ≤4 at 1 or 5 min
- Hypoxic encephalopathy
  - Volpe,[27] 1981
    - Not defined
  - Finer et al,[14] 1981
    - One of three criteria
      - Abnormal heart rate pattern (not defined)
      - Apgar score, ≤4 at 1 or 5 min
      - Need for immediate resuscitation or intubation
  - Amiel-Tison and Ellison, 1986*
    - One of four criteria
      - Fetal heart rate, <120 or >160 beats per min once (?) if by auscultation, prolonged (not defined) if by electronic monitoring
      - Repetitive heart rate decelerations (not defined)
      - Presence of meconium
      - Apgar score, <6 at 5 min
- Postasphyxial encephalopathy
  - Levene et al,[17] 1986
    - Diagnosis of "birth asphyxia" plus "good evidence (not defined) that asphyxia was the cause of neurological disturbance"
- Postasphyxia score
  - Lipper et al,[16] 1986
    - Apgar score, <6 plus one of the following
      - Bradycardia (not defined)
      - Variable or late heart rate decelerations (how many?)
      - Loss of beat-to-beat variability of fetal heart rate
      - Scalp or a cord pH, <7.2
      - Need for resuscitation
      - Meconium aspiration

*Dev Med Child Neurol. 1986;28:671-678.

distress" that was not further defined although case descriptions suggest that fetal distress was inferred on the basis of intubation at birth, fetal bradycardia or tachycardia during labor, in utero passage of meconium, or precipitous delivery.

Also in 1976, Ziegler and colleagues[13] described a group of term neonates with an encephalopathy ("cerebral distress syndrome") that was not related to malformation, infection, or erythroblastosis. They defined neonatal asphyxia in these infants by delay of the first cry (>2.5 minutes), low Apgar score, levels of pH or lactic acid, or need for resuscitation. The frequency of these characteristics among infants free of neonatal neurologic abnormalities is rarely reported.

Starting from variously preselected clinical samples, subsequent authors have discussed HIE without a definition[9] or with definitions that were vague[14-16] or circular.[17,18] Elements of the diagnosis for many workers have been electronic fetal-monitoring (EFM) characteristics and measures of acid-base balance; thus, they have built into the definition of NE a relationship to the characteristics that they take to be markers of asphyxia, thereby preventing an examination of the association between asphyxia and encephalopathy. Few workers specify unambiguous, objective, noncircular, and reproducible definitions or selection criteria by which to recognize infants with NE attributable to hypoxia, ischemia, or asphyxia.

Table 2.—Similarity of Characteristics Often Taken to Define 'Birth Asphyxia' and 'HIE'*

Characteristics	Birth Asphyxia	HIE
Depression of		
Tone†	+	+
Reflexes†		
Suck	+	+
Swallow	. . .	+
Moro's	+	+
Respiration†		
Difficulty with initiating repiration	+	. . .
Difficulty with maintaining respiration	. . .	+
Pulse rate†	+	. . .
Circulation/color†	+	. . .
Lethargy, stupor, coma	(+)	+
Seizure	. . .	+

*HIE indicates hypoxic-ischemic encephalopathy; plus sign, yes; and parenthetic plus sign, implicit but not explicit.

†Low Apgar score components.

Similarities Between the Putative *Cause* and the *Effect*

Another wrinkle in the logic of HIE is that the characteristics of the putative *cause*, ie, asphyxia, have a great deal in common with the characteristics of the putative *effect*, ie, NE (Table 2). The characteristics most often cited as markers of asphyxia are low Apgar scores and the component elements of low Apgar scores, including hypotonia, poor reflex responsivity, difficulty or delay with initiating and maintaining respiration, and bradycardia, and other abnormalities of the fetal heart rate, or the presence of meconium. The characteristics of NE are hypotonia, poor reflex responsivity (which can include autonomic reflex dysfunction), difficulty with maintaining respiration, and seizures. Consciousness, not examined as part of the Apgar score, might be assumed to be depressed in the apneic and very hypotonic infant. Thus, most of the characteristics cited are shared by putative cause and putative effect.

The Apgar score is a rapid standardized measure of neurologic depression during the first minutes of life. Low Apgar scores may be the result of drugs or toxins, immaturity, or infection,[19-21] or these scores may be associated with such antecedents, as low socioeconomic status, route of delivery, high parity,[22] maternal alcohol use,[23] and maternal illnesses, including coagulopathy, pulmonary tuberculosis, and hypothyroidism.[24] Low Apgar scores are unlikely to be causes of morbidity, but rather the results of prior causes. Indeed, they may be the earliest postnatal manifestations of an encephalopathy that is already present at birth.

If low Apgar scores and their correlates are part of the syndrome of NE and not acceptable as explanations for the NE, then to establish the cause of the encephalopathy requires identification of antecedents that are not part of the outcome.

ARE INDICATORS OF ASPHYXIA REGULARLY PRESENT IN NEONATES WITH ENCEPHALOPATHY?

Clinical Abnormalities of Labor and Delivery

If the majority of NE is truly secondary to birth asphyxia, then one might reasonably expect that "anoxigenic" obstetric complications would be powerful predictors of NE. Ziegler et al[13] and Amiel-Tison[25] described obstetric abnormalities in a substantial proportion of infants with NE, but they did not compare the frequency of the same factors in asymptomatic newborns. Neither group of investigators found symptomatic newborns to have a different outcome, depending on whether obstetric problems were identified. A Finnish report[26] observed diverse cerebral symptoms in the newborn to be associated with diverse characteristics of pregnancy, labor, and the newborn period; the proportion of infants who were premature and the overlap in risk factors were not stated. Volpe[27] noted that 30% of infants with encephalopathy, described as hypoxic-ischemic, had had no recognized abnormalities during labor.

At least one birth complication or sign of fetal distress (meconium in the amniotic fluid or fetal heart rate below 100 beats per minute) occurred in 74% of infants whose birth weight was greater than 2500 g and who had three or more signs compatible with NE, and in 61% of infants who had no signs of NE.[3] This is a difference, but not a great difference. Among infants in the same study whose births were uncomplicated and who showed no signs of fetal distress, 2.9% manifested sustained neonatal abnormalities consistent with NE, compared with a rate of 3.3% among infants with one or more birth complications or signs of fetal distress.

Obstetric Optimality Scores

Prechtl,[28] noting the weakness of the relationship between obstetric complications and neonatal neurologic morbidity and an "impression that complications do not operate as risk factors if they occur in isolation," invented an optimality measure. With the use of the Prechtl and Beintema neonatal neurologic examination and the Prechtl optimality concept, Touwen and coworkers[29] found that the obstetric characteristics that distinguished best between neurologically optimal and nonoptimal neonates were maternal proteinuria, prenatal care, gestational age, time to first cry, Apgar score, and transfer to a neonatal special care unit. None of these factors is best described as a complication of birth, and none of the complications examined proved to be important predictors of neonatal neurologic syndromes.

In the studies examined, some problem in pregnancy or birth was common but far from universal in the histories of children with neonatal neurologic symptoms, but birth problems were also fairly common in children free of neonatal symptoms. The limited evidence available does not document a powerful association of intrapartum complications with signs of NE.

Classic Signs of Fetal Distress

Meconium in the amniotic fluid and fetal bradycardia are the classic signs of fetal distress. Two reports that apparently overlapped in study population[30,31] indicated that half of term infants with neonatal seizures had meconium staining of the amniotic fluid, compared with 11% to 25% of controls. In other studies, the presence of meconium in the amniotic fluid was not related to neonatal neurologic abnormality[26,32] or pH.[32] Steer et al[33] found the major predictor of meconium in the amniotic fluid to be gestational age, and they observed so little coherence among the various measures that are usually taken to constitute "fetal distress" that they questioned the existence of such an entity.

The presence of meconium or of fetal bradycardia (heart rate <100 beats per minute) was associated with an increase in risk of cerebral palsy only in the small minority of infants whose Apgar score was low,[34] suggesting that neither meconium nor moderate bradycardia alone is a marker of serious fetal compromise.

Altshuler and Hyde[35] reported that meconium itself can induce constriction of umbilical and placental vessels sufficient to cause vascular necrosis of the placenta. The possibility that some component regularly or occasionally present in meconium may itself be injurious warrants further evaluation.

EFM

Electronic fetal (heart rate) monitoring in labor was introduced to help reduce the probability of intrapartum fetal death. Some obstetricians also offered the hope that EFM would permit medical attendants to recognize asphyxia early, enabling preventive interventions to "rescue" affected fetuses and thus prevent cerebral palsy and sharply decrease the frequency of mental retardation.[36] However, EFM does not appear to be superior to intermittent auscultation in decreasing neonatal morbidity.[37,38]

In the Dublin (Ireland) randomized clinical trial of fetal monitoring, infants who were assigned randomly to intermittent auscultation or to EFM with or without an option for fetal scalp pH did not differ in the rate of Apgar scores below 4 at 1 or 5 minutes.[39] In another study, EFM did not predict low 5-minute Apgar scores.[40]

Visser[41] reported that among growth-retarded fetuses, results of neonatal examination correlated better with heart rate patterns that were recorded before labor began than with intrapartum abnormalities. This and the repeated finding of an association between congenital anomalies and EFM abnormalities[42-44] are in keeping with the view that in some infants, EFM abnormalities reflect preexisting intracranial abnormalities.

A recent study has noted a relationship between late decelerations in the first stage of labor and neonatal neurologic status, but it did not report predictive values.[45] The sample for that study was selected by virtue of medical concern for the infants, and it is not clear that the analyses included birth weight or gestational age as potential confounders. A higher rate of neonatal seizures was seen in the intermittently auscultated group than in the EFM group in one study.[39] The seizure excess was limited to the relatively small subset of infants who were born after lengthy labors that were augmented with oxytocin, an observation that warrant examination in a fresh study.[46] Seven other studies have not shown that fetal heart rate monitoring lowers the risk of neonatal seizures.[37,38] In infants who were randomly assigned to EFM or intermittent auscultation, neonatal morbidity and developmental status were comparable at the age of 9 months.[47] The rate of later cerebral palsy was not lower in electronically monitored than in auscultated infants in two studies,[38,48] and it was, in fact, significantly higher among monitored preterm infants in one of these.[38] If this observation is confirmed, then an explanation should be sought. One possibility is that intra-amniotic infection, an important risk factor for cerebral palsy, may be more common in infants exposed to lengthy internal fetal monitoring.[49]

Acid-Base Measures

Some authors view umbilical artery acidosis or buffer base deficit as the best readily available marker of systemic hypoxia that occurs during the later stages of labor.[50] However, accumulated experience from a number of studies indicates that most infants with encephalopathy are not acidotic.[51-54] For example, in term infants with persistent hypotonia, 81% had pH_{ua} values over 7.15,[54] and cord blood gas measurements explained less than 1% of the variance in the score on a standardized neonatal neurologic examination.[30] In addition, most acidotic infants are not encephalopathic.[32,55,56]

Sykes and colleagues[57] in Oxfordshire, England, suggested that since pH and Apgar score were not strongly correlated, Apgar scoring should be abandoned. Follow-up of their cohort indicated no relationship between pH and measures of neurologic and psychologic function at the age of 4.5 years.[58]

It seems likely that with pH as with Apgar scores,[59,60] only extremely depressed scores are associated with an increase in risk of unfavorable neurologic outcome. Among 32 835 births with birth weights greater than 2500 g, the risk of death, neonatal seizures, or need for intensive care was increased only when the umbilical artery pH was below 7.05. Most of the risk was with pH below 7.00, and even at that level, the majority of infants had no neonatal complications.[61] Furthermore, preexisting vulnerabilities may interact with factors that produce acidosis in determining outcome: of 23 very acidotic infants (pH <7.00 with metabolic component; 1- and 5-minute Apgar scores ≤3), the only two who were symptomatic as neonates were infants with severe prenatal problems.[55]

In the light of these findings, we conclude as others have that the relationship of pH or base deficit to neonatal or to long-term neurologic disability does not appear to be strong.

Neonatal Seizures

Neonatal seizures are a part of the NE syndrome in its moderate or severe forms[4] and may indicate serious risk of adverse outcome.[62] But neonatal seizures are a heterogeneous group of disorders. Among neonatal seizures is a benign familial variety for which a gene locus may have been identified[63] and conditions of very unfavorable outlook, not related to asphyxia.[64] Many studies do not distinguish neonatal seizures that occur in isolation in infants who are otherwise well, or with only transient metabolic dysfunction, from seizures accompanied by other evidence of encephalopathy or by evidence of involvement of organs other than the central nervous system.

Some infants who are thought to have clinical seizures may not display electroencephalographic evidence of these, and electrical seizures are not necessarily accompanied by clinically recognizable manifestations.[18] It is not known whether clinical features or electroencephalographic characteristics are better predictors of handicap in surviving infants.

In series of infants with neonatal seizures, meconium staining of the amniotic fluid was absent in 28% to 53%,[30,31,65,66] and acidosis was absent in 60%.[67] In addition, intubation was not needed at birth by 65%, and 89% did not need subsequent ventilatory support.[68] Thus, even broad definitions of asphyxia or hypoxia were not met by most newborns with otherwise unexplained seizures.

The literature has stressed that most "asphyxial" seizures occur early.[30,67] The inference has been drawn[31] that most early seizures are therefore asphyxial. In one large study, of all the children with seizures in the nursery period, three quarters had them in the first 48 hours of life.[62] However, 61% of seizures in the first 2 days occurred in infants with Apgar scores of 7 or higher. "Thus, although depressed infants tended to have seizures early, about half of early neonatal seizures were in nondepressed infants."[62]

The more energetic the workup of newborn seizures, the more likely it is that nonasphyxial causes will be identified. For example, in a group of young children whose epilepsy began with neonatal seizures as early as 2 hours of age, positron emission tomography identified lesions that were later shown on neuropathologic examination to reflect defects in neuronal migration.[69] Even very early seizures, as well as continuing neurologic morbidity, can be the result of neuroanatomic defects that are present in the infant since the middle trimester of fetal life.

OTHER FEATURES THAT MAY BE HELPFUL IN RECOGNIZING WHEN NE IS ASPHYXIAL

Multisystem Involvement

In term newborns, the kidney and myocardium may be at least as vulnerable as the brain to impaired blood flow and oxygenation.[70-72] Impairment of systemic blood flow sufficient to damage the brain regularly also damages other organs in addition. Infants with NE but without multisystem involvement are unlikely to have their encephalopathy on the basis of intrapartum asphyxia. Perlman and Tack[73] reported that sustained oliguria and an elevated urinary β_2-microglobulin level (reflecting a renal origin of the oliguria) were predictors of neonatal seizures or cranial ultrasound abnormality, as well as of later abnormal neurologic status. However, encephalopathy with seizures accompanied by hematuria or oliguria and involvement of other organs, including gastrointestinal, genitourinary, and other systems, as well as the brain, can occur with embolization or coagulopathy,[74,75] thrombosis, or infectious (see below) or other conditions, so this constellation is not specific to asphyxial injury.

Other Markers

A variety of indicators have been described, including biochemical,[76-80] electroencephalographic,[2,81-83] and evoked potentials,[84] neuroimaging, including ultrasound[85,86] and magnetic resonance imaging,[87-89] magnetic resonance spectroscopy and near-infrared spectroscopy,[90-92] and impaired regulation of cerebral blood flow.[92-94] Many of these techniques are not widely available, and few can identify abnormalities as soon after delivery as will be required for therapies directed at prevention of consequences of birth asphyxia.

WHAT ELSE CAN CAUSE SIGNS OF NE?

Many features of the NE that are so commonly attributed to asphyxia, such as neonatal hypotonia,[95] difficulty with feeding,[96] and neonatal respiratory delay,[97] may have other explanations. In congenital myotonic dystrophy[98] and in the Prader-Willi syndrome,[99] for example, abnormalities of pregnancy and birth and low Apgar scores, hypotonia, poor suck, and need for respiratory assistance are relatively frequent. Focal cerebral infarction,[100] metabolic disorders of a wide variety,[101] and trauma[102] can produce many of the same signs. Diagnoses of birth asphyxia are often made clinically in infants with these other conditions.

Chorioamnionitis is associated with low Apgar scores[23,24] and prolonged labor[103] and perhaps with progressive metabolic acidosis, although evidence on this last point is not consistent. Chorioamnionitis is a risk factor for cystic lesions on ultrasound that are in turn important predictors of cerebral palsy.[104] Organisms that cause chorioamnionitis may be fastidious and evade routine bacteriologic identification and be recognized only by means of histology.[105,106] Chorioamnionitis is also a precursor of neonatal sepsis, which can produce systemic and neurologic illness, including neonatal seizures. Since infection can mimic so many of the features of HIE, the distinction between infectious and asphyxial encephalopathic illnesses in the neonate, and a judgment as to the contribution of each if both are present, may be difficult.

For these and other disorders, differential diagnosis rests on recognition of specific features that are not always prominent in the newborn, even if carefully sought. Although many of these conditions are uncommon individually, no one knows what proportion of all HIE that they represent.

NE AND THE FOURTH DIMENSION[107]: HOW QUICKLY AFTER BIRTH CAN A CONFIDENT CONCLUSION BE REACHED THAT A SEVERE INSULT HAS OCCURRED AND THAT ASPHYXIA IS ITS BASIS?

A number of investigators[2,13,65,108] have written that infants who have truly suffered cerebral injury due to asphyxia at birth display a characteristic evolution of signs over time. These observations are reasonably consistent and of great importance to understanding NE. However, this evolution has not yet been captured and quantified in a formulation that permits its predictive use.[4] Furthermore, and a critical problem for planning for future studies of early therapeutic interventions, most of the characteristics that permit a confident recognition of the severity of NE, and perhaps of an asphyxial origin, are features of the clinical course that cannot be recognized until many hours or days after birth. Yet, most currently proposed interventions must take place very soon after delivery.

COMMENT

The signs of NE are nonspecific. Birth asphyxia sufficient to produce NE is not easy to distinguish from other causes as events unfold in the early minutes and hours after delivery. The markers that are often used as indicators of asphyxia, such as low Apgar scores and their correlates, including hypotonia and delayed respiration, are not specific to asphyxia and may themselves be early evidence of encephalopathy predating birth, or of other kinds of neonatal illness. The usual measures of perinatal asphyxia do not correlate well with one another and are not good predictors of neurologic condition even within the neonatal period.

Most severely asphyxiated children who survive are later clinically normal.[59,60,109] Agents proposed for treating birth asphyxia are powerful and possess risks that are known from animal testing, with effects in the human that are not fully predictable. Proposers of clinical trials of new therapies for birth asphyxia will be under a strong obligation to judge that the treatment is not worse than the disease.

For future clinical trials of agents for birth asphyxia, then, it will be necessary to select as candidates infants who are at high risk of encephalopathy, neonatal and subsequent, because of asphyxia. It will probably be necessary to make decisions about magnitude and cause of risk on the basis of information in hand within the first hour or two of life. To what extent is that feasible today? In preparation for the anticipated clinical trials for birth asphyxia, we recommend consideration of tests of the predictive validity of clinical and technologic markers specific to asphyxia that are available soon after birth.

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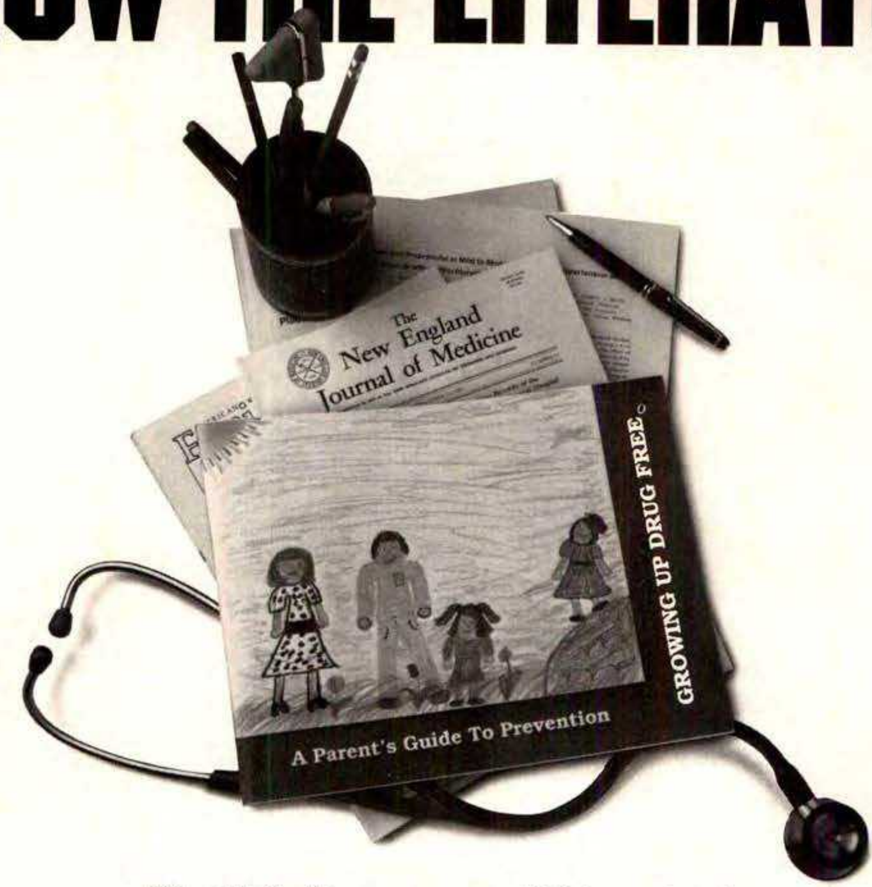
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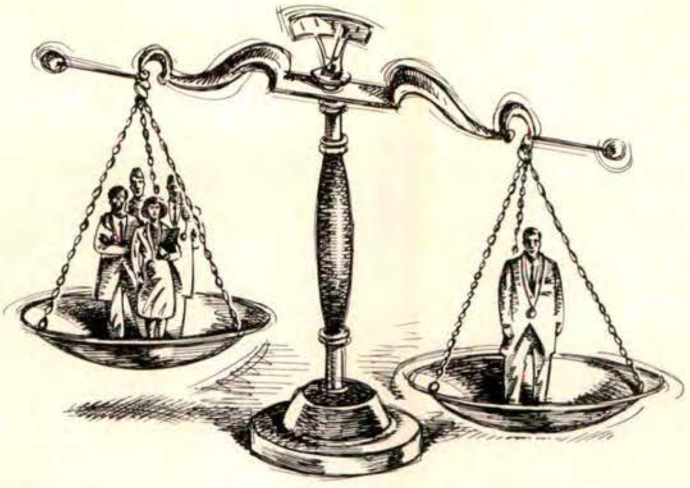

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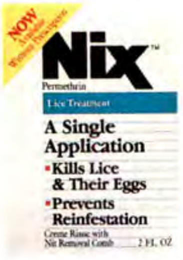

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